Studies of the Mechanisms of Sacral Nerve Stimulation for Faecal Incontinence: Investigations of Anorectal and Pelvic Floor Physiology and Function

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Dedication

To Ayman – *you are always in my thoughts*

To Mr Shandall – *for his sincere advice*

Declaration

I, Mostafa R. E. Abdel-Halim confirm that the work presented in this thesis is my own. All the work was undertaken at the University College London Hospital.

Abstract

Studies of Sacral Nerve Stimulation (SNS) have demonstrated significant symptom improvement in Faecal Incontinence (FI); however, mechanisms of action remain poorly understood. Various authors have examined anorectal physiological parameters with SNS; and apart from an observed increase in squeeze pressures, findings were mostly inconsistent. It is currently believed that effects are mediated through neuromodulation.

Identification of the involved neuronal pathways and the associated changes at the level of the target organ can further inform the process of patient selection for this costly treatment. The aim of this thesis was to examine potential SNS mechanisms by studying its effects on the sphincteric and suprasphincteric properties utilising physiological and structural tests.

A total of 30 patients (29 female, median age 49 years) with intractable FI undergoing temporary SNS were recruited into four different studies designed to examine associated physiological and structural changes.

The study of rectal properties revealed no change in rectal compliance following stimulation. However, rectal pressures associated with urge perception and maximally tolerated distension were significantly increased; predominantly in clinical responders.

Anal squeeze pressures were significantly increased after stimulation in both responders and nonresponders. However, an increase in resting pressure was only noted in responders.

Furthermore, Recto-Anal Inhibitory Reflex (RAIR) recovery time was significantly shorter after stimulation. An acute ON/OFF alteration of stimulation did not result in an acute change in anal pressures or RAIR parameters.

Magnetic Resonance Proctography revealed a trend of reduced duration of rectal emptying after stimulation. Furthermore; it has suggested that more efficient contrast evacuation occurs after SNS.

Mechanisms of SNS are most probably complex and multi-factorial. The observed changes in rectal sensory thresholds, RAIR recovery time and rectal evacuation in this study suggest that SNS influences the anorectal autonomic function and that it has an afferent-mediated mechanism.

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Glossary of Abbreviations

ARA	Ano-Rectal Angle
ARP	Ano-Rectal Physiology
BOP	Basal Operating Pressure
CGRP	Calcitonin Gene Related Peptide
CNS	Central Nervous System
EAS	External Anal Sphincter
EAUS	Endo-Anal Ultra Sound
EEG	Electroencephalogram
EMG	Electromyogram
ENS	Enteric Nervous System
ESP	Evoked Sacral Potentials
EUD	Earliest Urge to Defaecate
FI	Faecal Incontinence
FS	First Sensation (rectal sensory threshold)
FU	Follow Up
GABA	Gamma Amino Butyric Acid
GI	Gastro-Intestinal
HAPS	High Amplitude Propagating Sequences
HRM	High Resolution Manometry
Hz	Hertz
IAS	Internal Anal Sphincter
IGLEs	Intra-Ganglionic Laminar Endings
mA	milli Ampere
MDP	Minimal Distending Pressure

MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MSNS	Magnetic Sacral Nerve Stimulation
MTV	Maximum Tolerated Volume
NICE	National Institute for Clinical Excellence
PCL	Pubo-Coccygeal Line
PNE	Peripheral Nerve Evaluation (temporary SNS in the context of SNS)
PNML	Pudendal Nerve Motor Latency
Press.	Pressure
PS	Propagating Sequences
Pt ID	Patient Identification
PTNS	Posterior Tibial Nerve Stimulation
Qzt	Quasitrapezpoidal
RDMBF	Rectal Doppler Mucosal Blood Flow
RAIR	Recto-Anal Inhibitory Reflex
SF-36 QoL	Short Form-36 Quality of Life Questionnaire
SCI	Spinal Cord Injury
SCS	Spinal Cord Stimulation
SNS	Sacral Nerve Stimulation
STARR	Stapled Trans-Anal Rectal Resection
Stim.	Stimulation
U	Urge (rectal sensory threshold)
VIP	Vasoactive Intestinal Peptide
Vol.	Volume

Communications arising from the Thesis

Published papers

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Oral presentations

Oct 2010 Blinded examination of the effects of acute alteration of stimulation status on anal manometry during the course of temporary sacral nerve stimulation for faecal incontinence.
MRE Abdel-Halim, R Cohen, A Emmanuel.
United European Gastroenterology Week (UEGW) 2010. Barcelona.

Mar 2010 Assessment of rectal compliance and sensory function following temporary sacral nerve stimulation
MRE Abdel-Halim, A Windsor, CRG Cohen, AV Emmanuel.
British Society of Gastroenterology (BSG) meeting, Liverpool.

Poster presentations

Jun 2011 Magnetic Resonance Proctography demonstrates improved rectal emptying following temporary SNS – a mechanistic study
M R E Abdel-Halim, S Taylor, J Crosbie, C R G Cohen, A. Emmanuel.
ACPGBI annual meeting, Birmingham.

Oct 2010 Rectal Sensorimotor changes with Sacral Nerve Stimulation.
MRE Abdel-Halim, D Chatoor, A Windsor, R Cohen, A Emmanuel.
United European Gastroenterology Week (UEGW) 2010. Barcelona.

Oct 2010 Influence of Sacral Nerve Stimulation on the intrinsic anorectal reflexes.
MRE Abdel-Halim, J Crosbie, R Cohen, A Emmanuel.
United European Gastroenterology Week (UEGW) 2010. Barcelona.

Sep 2010 Rectal physiological properties following temporary sacral nerve stimulation.
MRE Abdel-Halim, J Crosbie, A Windsor, CRG Cohen, AV Emmanuel.
European Society of Coloproctology (ESCP) Annual Meeting, Sorrento.

Jun 2010 Rectal Compliance Does Not Change With Successful Sacral Nerve Stimulation.
MRE Abdel-Halim, A Windsor, CRG Cohen, AV Emmanuel.
ACPGBI annual meeting, Bournemouth.

Chapter 1

Relevant Anatomy & Physiology

1.1 Chapter layout

In this chapter I present a brief summary of the relevant anorectal anatomy and physiology. Firstly, I present a description of the gross anatomy of the anorectum then I describe its nerve supply in some detail as clear understanding of this is crucial to the hypotheses laid in this work.

I then present a summary of the neuronal control of intestinal functions highlighting the interactions between the enteric and central nervous system. I also present few paragraphs on relevant physiology including a brief description of physiology of defecation, rectal sensations and compliance.

1.2 Descriptive anatomy of the anorectum and pelvic floor[1-3]

1.2.1 Anorectum

The rectum commences where the taenia coli fuse to form a continuous longitudinal muscle layer. This is usually at the level of the sacral promontory. The rectum is about 15cm long. It is only partly covered by the peritoneum which reflects off the anterior aspect of its middle third forming the recto-vesical and recto-uterine (of Douglas) pouches in men and women respectively. The rectum sits in and follows the hollow of the lower sacrum before it curves backwards and inferiorly at the level of the pelvic floor to form the anal canal.

The anal canal is 4 to 6 cm in length but is shorter in females. From an embryological perspective the anal canal can be defined as the part extending from the anal valves to the anal margin only as the anal valves and the dentate line represent the site of breakdown of the cloacal membrane during development.

The epithelial lining of the anal canal progresses as follows (caudal-cranial direction): stratified squamous keratinized epithelium with hair follicles, sweat and sebaceous glands to stratified squamous non-keratinized epithelium without hair follicles or glands to the Anal Transition Zone (variable epithelial structure with mixed columnar and stratified squamous epithelium) to finally rectal mucosa-type columnar epithelium.

1.2.2 Internal Anal Sphincter (IAS)

The internal anal sphincter (IAS) which is formed of smooth muscles is a continuation of the circular layer of the muscularis propria of the rectum. It ends with a well-defined rounded edge 6-8 mm above the anal margin. The IAS thickness is approximately 2-3 mm on endoluminal imaging; however, it increases with age in both sexes.

1.2.3 External Anal Sphincter (EAS)

The external anal sphincter complex (EAS) is composed of a cylinder of striated muscle. The lower border of the EAS extends beyond the inferior margin of the IAS to become subcutaneous. It is currently understood that the EAS is made up of a series of three

loops. The upper loop is made up of the EAS and puborectalis and its limbs are attached to the pubis. The middle loop is made up of the mid-portion of the EAS and is attached posteriorly to the coccyx. The basal loop is perforated by fibres from the longitudinal muscle layer. The thickness of the EAS is around 4mm on endoluminal imaging.

The thin fat containing inter-sphincteric space also contains the fibres of continuation of the longitudinal muscle layer of the rectum which blends with pubococcygeus at the anorectal junction and traverse caudally. The fibres lie within the intersphincteric space and break up opposite the lower border of the IAS forming fibrous septae which fan out through the EAS ultimately attaching to the skin of the perianal region.

1.2.4 The pelvic floor

The pelvic floor is a complex musculo-fascial body which supports the structure and function of the viscera which traverse it. It is formed primarily of the levator ani; a compound muscular structure. However, in front of the rectoanal junction lies the perineal body and posterior to it lies the anococcygeal body or plate which extends from the anal canal to the caudal part of the vertebral column. Also directly below the levator ani plate in the anterior pelvic outlet lies the triangular fibromuscular perineal membrane (or urogential diaphragm). The most superficial component of the pelvic floor are the superficial transverse perineii and the other external genitalia muscles namely bulbospongiosus and ischiocavernosus.

The levator ani muscle which has a linear origin extending from the body of the pubis to the ischeal spine is conventionally divided into four parts; although *ischiococcygeus* is a rudimentary muscle in man and represents little more than the sacrospinous ligament. *Puborectalis* arises from the lower part of the back of the symphysis pubis and forms a loop around the recto-anal junction with its fibres at this point closely related to the deep part of the external sphincter. Puborectalis has no posterior attachment to the vertebral column and the loop acts to pull the rectoanal flexure forward accentuating the angle. *Pubococcygeus* arises from the pubis and the anterior part of the obturator fascia and its fibres are directed horizontally backwards attaching mainly to a flattened tendon which inserts behind the rectum on the anterior surface of the coccyx. Iliococcygeus is a thin muscle which takes origin from the posterior part of the obturator fascia and the medial surface of the ischial spine; it partially overlaps pubococcygeus to insert below it on the lateral surfaces of the terminal portion of the coccyx and the anococcygeal raphe.

The perineal body is a midline-situated fibromuscular wedge between the anal canal and the urogenital viscera. It acts as a site of attachment of many structures including the external anal sphincter, the perineal membrane and the superficial transverse perineii muscles.

1.3 Nerve supply of the anorectum and the pelvic floor

1.3.1 Nerve supply of the rectum

The nerve supply of the rectum is by the autonomic nervous system. Sympathetic supply is by branches of the superior hypogastric plexus and by fibres accompanying the inferior mesenteric and superior rectal arteries . Parasympathetic supply is from S2-S4 segments through the inferior hypogastric plexuses (by the pelvic splanchnic nerves).

1.3.2 Nerve supply of the anal canal and anal sphincters

The neurovascular supply of the superior two-thirds of the anus which embryological has a hindgut origin (the cloacal anus) is distinct from that of the inferior one-third which has an ectodermal origin (the proctodermal anus).

Nerve supply to the superior two-thirds of the anal mucosa is by the autonomic nervous system, for the lower part is by the inferior rectal nerve which is a somatic nerve.

The internal sphincter is supplied by the autonomic nervous system. The sympathetic fibres (from the inferior pelvic plexus) are stimulatory and pass along the superior rectal artery. The parasympathetic fibres are inhibitory (from S2 to S4) and they pass through the inferior pelvic plexus and splanchnic nerves.

The external sphincter has somatic innervation (S2 to4) through the inferior rectal branch of the pudendal nerve (S2, S3) and the perineal branch of the fourth sacral nerve (S4).

The puborectalis has somatic innervations through S3 and S4 by the levator ani nerve and by the pudendal nerve.

1.3.3 Nerve supply of the pelvic floor

The pelvic floor has both somatic and autonomic nerve supply.

The somatic nerve supply is through branches of the sacral plexus, namely the pudendal nerve which courses inferior to the pelvic floor and the levator ani nerve which courses superior to the pelvic floor.

The autonomic nerve supply to the pelvic floor includes the parasympathetic supply through the pelvic splanchnic nerves or nervi erigentes which arises from S2-S4. The sympathetic nerves arising from T10-T12 course through the sympathetic chain and pre-aortic plexus to the hypogastric nerve which subsequently approaches the pelvic plexus (or inferior hypogastric plexus) which is a plexus of the sympathetic and parasympathetic nerves which supply the pelvic organs.

1.3.4 Summary of anorectal nerve supply

As can be noted, there appears to be a dual peripheral nerve supply (branches of the pudendal nerve and direct branches of the sacral nerves) to the muscles of the continence mechanism. Therefore, stimulation of the sacral spinal nerve can potentially excite both nerves. The basis for SNS is that by stimulating these sacral nerves, additional residual function of an inadequate pelvic floor musculature and pelvic organs can be recruited[4].

Table 1.1 Summary of anorectal nerve supply

	Sensory	Motor
Somatic	-sensations from perineum and external genitalia -sensations from the lower third of anal canal	-motor to pelvic floor -motor to external anal sphincter
Parasympathetic	-distension sensations from the rectum and anus -pain sensations from anus	-excitatory to colonic motility -inhibitory to internal anal sphincter -supplies pelvic floor
Sympathetic	-pain sensations from anus and rectum	-inhibitory to colonic motility -excitatory to internal anal sphincter -supplies pelvic floor

1.4 Neuronal control of intestinal function [5]

The alimentary tract motility is driven by an intrinsic system of enteric nerves. However, these are not completely independent. The enteric nervous system controls the smooth

muscle activity while under control of the central nervous system via efferent and afferent nerves from the autonomic nervous system. Components of the autonomic nervous system act as the link between the enteric nervous system and the central nervous system. The interaction occurs at various levels (the gut-brain axis) but the exact details of these interactions are not yet fully delineated.

The function of the intestine is in a state of continuous change and it is under constant modulation. Constant sensory-motor integration takes place at the level of the intra-mural plexuses, in the pre-vertebral sympathetic ganglia and in the Central Nervous System (CNS).

Figure 1.1 shows a diagrammatic representation of the relationship between the enteric and the central nervous systems.

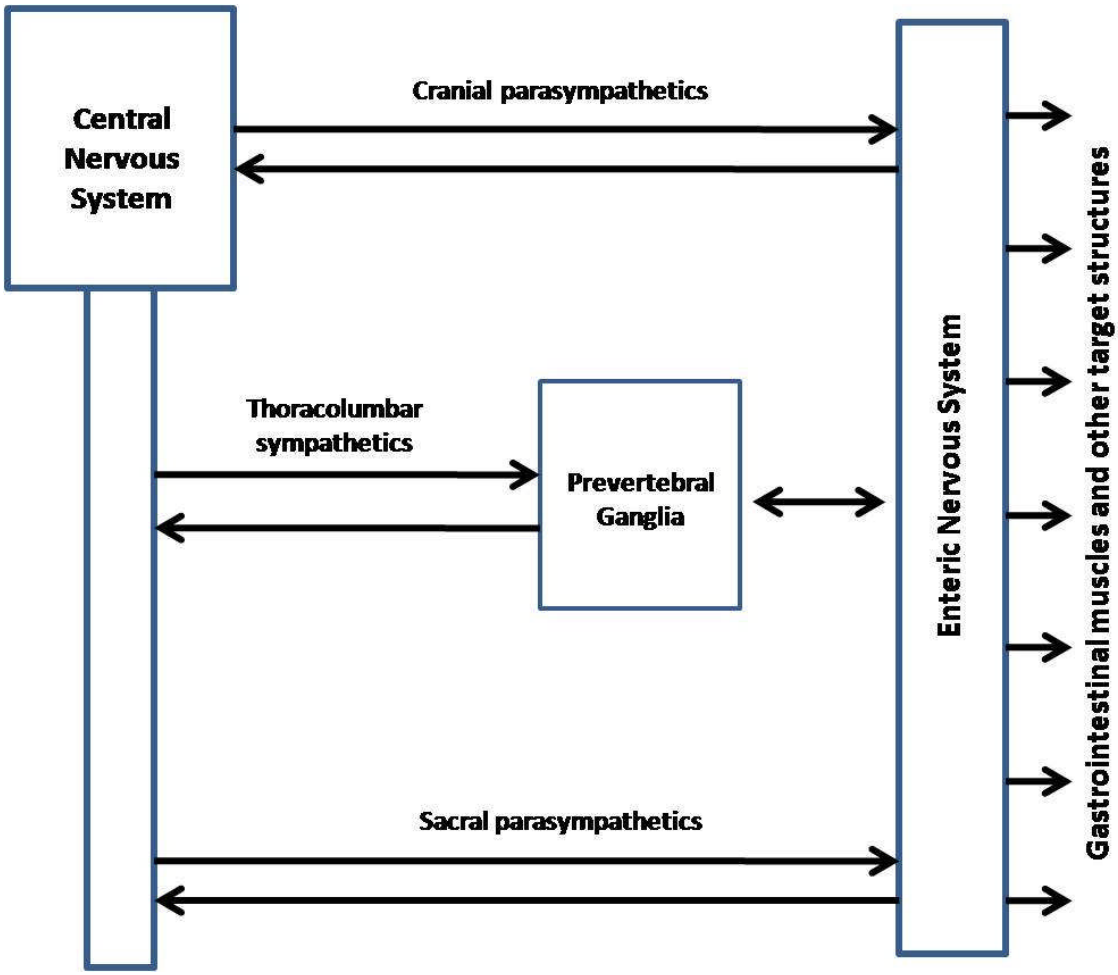

Figure 1.1 – Diagrammatic representation of CNS and ENS interactions

1.4.1 The intrinsic enteric system

The enteric system is composed of two ganglionated plexuses: the submucosal plexus which is situated within the submucosa; and the myenteric plexus which is situated between the inner circular and outer longitudinal muscle layers.

The submucosal plexus serves mainly a secretomotor purpose but it also has a sensory component and it innervates the muscularis mucosa[6].

The myenteric plexus contains motor neurons and it innervates the circular and longitudinal layers which are responsible for intestinal peristalsis.

In addition to the conventional neurotransmitters (Acetylcholine and Noradrenaline), the neurons of the intrinsic enteric nervous system release a large number of neuropeptides including substance P, Vasoactive Intestinal Peptide (VIP), γ-amino butyric acid (GABA), Serotonin, somatostatin and nitric oxide [7, 8].

1.4.2 The extrinsic nerves to the gut

The nerves which connect the CNS to the gut constitute two principal groups: The Cranio-Sacral system (the parasympathetic supply), and the Thoraco-Lumbar system (the sympathetic supply).

a) Parasympathetic system:

The influence of the parasympathetic system on the intestine is mainly excitatory motor influence (leading to increased bowel motility) with inhibitory effect on the internal anal sphincter (IAS relaxation).

Parasympathetic nerve supply to the bowel is derived from two sources: a) from the vagus nerves; b) from the parasympathetics arising from the sacral roots (S2-S4). The

domain of the vagus extends to the right colon. The sacral parasympathetics supply the left colon and anorectum through the pelvic and pudendal nerves[9].

b) Sympathetic system:

The sympathetic supply originates from the thoracic and lumbar segments of the spinal cord. It traverses through the splanchnic nerves to the prevertebral, celiac, superior and inferior mesenteric ganglia. From these ganglia, the nerves pass alongside the mesenteric vessels to reach the gut.

The supply to the small bowel, ascending and transverse colon arises from the thoracic segments (T5-T12), whilst the output from the lumbar segments (L1-L3) is distributed to the left colon and the anorectum.

The sympathetic system is generally inhibitory to gut motility and excitatory to the IAS.

1.4.3 Gut reflex motor responses[5]

There are a number of sensory structures in the gut. The intraganglionic laminar endings (IGLEs) found in the myenteric plexus of the oesophagus and stomach[10] are established sensory receptors. Other undifferentiated sensory neurons are present in the intestinal epithelium throughout.

Reflex motor responses can be demonstrated in response to both mechanical and chemical stimuli. Mediation of these reflexes can be through local or central pathways. The following are the best known of such reflexes within the gut:

a) Reflex oesophageal peristalsis after oesophageal distension:

Distension of the distal oesophagus leads to reflex oesophageal peristalsis and oesophageo-gastric sphincter relaxation. This is mediated both locally and centrally.

b) Reflex relaxation of the stomach with increased gastric volume:

The reflex expansion of the stomach during eating to accommodate the ingested volume is mediated both locally and centrally.

c) Reflex control of gastric emptying:

Certain substances on reaching the duodenum lead to slowing of gastric emptying. This is thought to be reflexly mediated, however, the exact pathways are not fully known.

d) Reflex intestinal peristalsis:

Intestinal distension leads to peristaltic waves. This is an intrinsic mediated reflex.

e) Reflex relaxation of the internal anal sphincter (RAIR):

Distension of the rectum leads to relaxation of the internal anal sphincter (the Recto Anal Inhibitory Reflex). The pathways of this reflex are presumed to be intrinsic.

1.5 Relevant physiological topics

In the following section I will briefly discuss the normal physiology of defecation as well as the physiology of rectal sensory function and rectal compliance. I will also briefly mention the various recognized types of nerve fibres based on their threshold to electric stimulation which is significantly relevant to the topic of the project.

1.5.1 Physiology of defecation[11, 12]

The maintenance of continence is not the function of anal sphincters only. It is the product of significant coordination between the rectum as a reservoir and the pelvic floor as a sphincter as well as an active muscular player in the process of defecation. There is growing evidence that abnormal rectal reflexes and sensorimotor dysfunction are key factors in the pathophysiology of faecal incontinence [13, 14].

The process of defecation starts by the cortical awareness of the sense of filling of the rectum. When the social settings allow, the individual adopts the suitable body positioning and the cortex allows the autonomic reflexes to go ahead. This starts by the reflex relaxation of the anal sphincters and the pelvic floor. This together with the increased intra-abdominal pressure through the increased tension in the abdominal wall muscles leads to the delivery of some rectal contents to the lower rectum and anal canal. This reflexly initiates the giant rectosigmoid contractions which occur until the rectum is empty. This reflex occurs at a spinal level.

Two aspects of the role of the rectum in this process, namely rectal sensory function and rectal compliance are further detailed below.

1.5.2 Rectal sensory function

Full understanding of the types and functions of rectal receptors is still lacking. IGLEs are known to be present in the upper gastrointestinal tract; however, recent animal work has revealed that the rectum contains functionally unique IGLEs [15]. The rectal distension is certainly associated with the perception of rectal filling and is associated with specific anorectal reflexes. Although the nature of the mediating receptors is not fully delineated, specialized mechanoreceptors are most probably responsible.

On another level, immunohistochemical studies have revealed the presence of specialized chemo- and mechano- receptors in the rectal mucosa [16, 17]. These are thought to be increased in number and their expression in patients with rectal hypersensitivity [17].

1.5.3 Rectal compliance

The phenomenon of receptive relaxation is a property of rectal wall musculature and it defines the rectum as a reservoir which is a crucial component of the defecation process. Given a slow filling rate the intraluminal rectal pressure does not increase until the maximum tolerated volume is approached. Rectal compliance measurement therefore reflects a measure of the combined sensorimotor function of the rectum.

Alterations in rectal compliance can be due to rectal hypersensitivity which results in significantly low maximally tolerated volumes or changes in rectal wall contractility. Abnormal rectal compliance have been documented in patients with anorectal dysfunction but interpretation of results can be problematic due to the lack of standardized protocols for measurement and the contribution of abnormal rectal sensations[11].

Chapter 2

Faecal Incontinence

2.1 Chapter layout

In this chapter I present a summary of the topics relevant to the subject of Faecal Incontinence (FI). I firstly, clarify the definition I used in this study and present a summary of my understanding of its aetiology and the clinical assessment and investigations undertaken in patients with this presentation, in a way which reflects the current literature as well as the standards adopted in my research unit.

I have reviewed the treatments available and presented these in a way that reflects treatment options classified according to mechanism of action and target function rather than according to the conventional classification of medical versus surgical options.

2.2 Definitions

Faecal incontinence or the involuntary loss of solid or liquid faecal material is a hugely incapacitating condition which results from disruption of a finely balanced physiological mechanism. It can result in progressive isolation and loss of individual potential with devastating psychosocial consequences.

The term Anal Incontinence is often used to also include the involuntary loss of flatus. This subtle differentiation in terminology was not strictly respected in this work, with the consideration that flatus incontinence is also included within the spectrum of events covered by the term faecal incontinence. This is the case in most grading systems for FI.

Therefore, the definition adopted for the term FI in this project was: 'the involuntary loss of solid or liquid faecal material or flatus'.

2.3 Introduction

Faecal incontinence is a challenging condition to treat and patients often have to overcome taboos in order to present to their doctor for treatment. The situation is often challenging to the physician and relevant knowledge among practitioners in the community is often lacking. Patients usually face options of either simple ineffective containment measures or major interventional procedures. However, more recently, a number of effective minimally invasive treatment options have emerged.

Treatment strategies should aim at reducing the burden of incontinence so that quality of life is improved. However, often definitive treatment is not possible and the aim becomes to help the patient cope with their symptoms.

2.4 Epidemiology

Faecal incontinence is not an uncommon disorder amongst the general population with community studies demonstrating prevalences of around 1.4 to 2.2% of the general population[18-20].

Prevalence significantly increases with ageing. Some studies have demonstrated a prevalence of 6-7% in the elderly population in the community [21] and up to around 10% of institutionalised elderly population[22].

In addition to the age-related difference in prevalence, there appear to be a higher prevalence in women in comparison with men in the middle-age and elderly groups[18, 23]. This is most likely related to obstetric factors which are a significant risk factor for development of FI.

2.5 Aetiology

There are numerous causes of FI, with any disruption to the physiological mechanism of anorectal function potentially leading to incontinence.

The sphincter-centric approach is better replaced with a more holistic understanding of aetiology as disruptions to normal physiology at any level. With this view, the state of incontinence becomes an extreme end on a spectrum which is usually balanced in the middle; the other end of the spectrum being 'difficulty in evacuation'.

I have attempted to include all common causes in the following classification. However, it is to be noted that a single aetiology might be causative through more than one mechanism.

2.5.1 Altered stool consistency (diaorrheal states)

1- Inflammatory bowel diseases

2- Infectious diaorrhea

3- Malabsorption syndromes

4- Short gut syndrome

5- Laxative abuse

6- Irritable Bowel Syndrome

2.5.2 Inadequate rectal reservoir or compliance

1- Inflammatory bowel disease

2- Radiation enteritis

3- Surgical resection of the reservoir:

   a- Low anterior resection of the rectum

   b- Ileoanal pouch surgery

4- Rectal ischaemia

5- Rectal neoplasia

6- Extrinsic rectal compression

7- Scleroderma and other Collagen disorders

2.5.3 Altered rectal sensory function or motility

1- Cerebrovascular stroke

2- Central neurological trauma or neoplasia

3- Multiple sclerosis

4- Tabes dorsalis

5- Spina bifida

6- Myelomeningocele

7- Dementia

8- Peripheral neuropathy

9- Impaired motility and resulting overflow incontinence:

a- Faecal impaction

b- Anti-motility drugs

c- Psychotropic drugs

10- Rectal hypermotility syndrome

2.5.4 Altered sphincter or pelvic floor mechanism

I) Anatomical or mechanical deficit:

1- Obstetric sphincter injury

2- Iatrogenic injury post anorectal surgery:

a- Anal fistula surgery (lay open procedures)

b- Haemorrhoidectomy

c- Sphincterotomy

d- Dilatation or anal stretch

3- Trauma

4- Neoplasia involving the sphincter

5- Congenital defects of the sphincter and pelvic floor:

a- Imperforate anus

b- Anal agenesis

II) Neurological deficit:

1- Neurogenic incontinence:

a- Pudendal neuropathy

b- Post vaginal delivery

2- Injury to spinal cord (cauda equina) or pelvic floor nerves (e.g. pelvic surgery)

3- Spina bifida and myelomeningocele

4- Diabetic neuropathy

III) Functional deficit:

1- Ageing

2- Sphincter atrophy

3- Prolonged rectal prolapse

4- Increased body mass index

Commonest causes are reported to be obstetric and iatrogenic sphincter trauma, degenerative causes and rectal and pelvic organ prolapse[24].

2.5.5 Obstetric trauma and its risk factors

Obstetric perineal trauma remains the commonest aetiological factor for faecal incontinence in women[24]. The incidence of developing FI after childbirth is reported to

be around 13% in primigravidas and 23% in multigravidas[25]. Patients can develop occult injuries and remain initially asymptomatic for a period of time.

A number of risk factors for obstetric perineal trauma have been identified. Those mainly include: primiparous delivery, forceps delivery, birth weight of > 4Kg and occipito-posterior position at delivery [25-27]. Some studies have recognised prolonged second stage of labour as a risk factor for perineal trauma [28]. Systematic review of the evidence suggested that routine episiotomy is associated with less incidence of anterior perineal trauma but not with less incidence of anal sphincter injury raising a question about the benefit of its routine use[29]. Other reviews have identified episiotomy as a risk factor for posterior perineal trauma [26, 30, 31].

2.6 Grading and classification

2.6.1 Grading of severity

Incontinence can be classified to minor or major according to the resultant burden of symptoms and degree of interference with quality of life. A number of grading questionnaires have been designed aiming at quantifying the extent of symptoms into a numeric analogue assessment. The most widely used are the Pescatori score [32], Wexner score [33], Vaizey score and the American Medical Systems' score (AMS score).

2.6.2 Classification according to the predominant clinical feature

Clinical history and examination is of paramount importance when assessing patients with faecal incontinence. Faecal incontinence can be generally classified according to the predominant feature into either Urge or Passive incontinence. However symptoms can often be combined.

2.6.2.1 Urge faecal incontinence:

This describes the inability to defer the act of defecation to such an extent that an involuntary loss occurs. Compromised external sphincter function is usually the main underlying problem[34, 35].

2.6.2.2 Passive faecal incontinence:

This presents as involuntary loss to variable degrees without conscious awareness. This is usually a feature of compromised internal sphincter function[34].

2.7 Clinical assessment

2.7.1 Clinical history

Careful clinical history is important. It is often required to tease out the complaints voiced by the patient and establish the presence of the problem in the first instance, as often patients do not verbalise the nature of the problem directly. In such circumstances,

the distressing problem of incontinence might remain unaddressed or be mistreated with consequences, if the physician omits detailed clear history taking and enquiry.

The nature of the incontinence and whether it is predominantly an urge or passive leakage sheds light on the potential pathophysiology as explained above. Detailed history will also allow the differentiation of perineal soiling or mucus staining which can result from the presence of haemorrhoidal or rectal mucosal prolapse, fistula-in-ano or perineal sexually transmitted lesions.

History of any precipitating factors and detailed obstetric history in female patients are also of great importance in delineating the problem. An essential part of the history taking is establishing the extent of disruption and affliction on the patient's quality of life and ability to pursue their daily activities and their degree of willingness to undergo an invasive intervention to address the problem. This will help direct treatment strategies which are primarily aimed at improving patients' quality of life and coping mechanisms.

2.7.2 Clinical Examination

Inspection of the peri-anal area may reveal the presence of skin excoriation from exposure to faecal matter. Other abnormalities like haemorrhoidal or rectal mucosal prolapse may be diagnosed. Perineal scarring and small or absent perineal body would suggest previous obstetric perineal trauma.

The examiner should also check for rectal or pelvic organ prolapse on straining. Digital rectal examination enables the examiner to assess: a) the bulk of the sphincter, b) the presence of palpable defects, c) the tone of the sphincter, d) the quality of the squeeze function, e) the presence of any rectal masses or rectocele, and f) observation of pelvic floor dyssynergia.

2.8 Investigations

Following detailed history and thorough clinical examination, full assessment requires complementary physiological studies and structural assessment.

2.8.1 Physiological studies

Numerous studies are currently available to assess and provide detailed information on various aspects of anorectal physiology. The clinical value of some of these tests is however still undetermined and clinical decisions on management are often informed by the clinical evaluation and less so with physiological results.

Physiological tests include the following:

2.8.1.1 Anal manometry

Different methods of measuring anal sphincter pressures can be applied[36]. The most widely used device is the water-perfused multi-channel catheter [37].

Anal manometry enables the measurement of the resting anal pressure (primarily reflective of internal sphincter function[38]), and the voluntary squeeze pressure (reflective of external sphincter function[38]). Additionally other more controversial aspects of sphincter function, namely the functional anal canal length and endurance squeeze pressure can also be measured[24].

Unfortunately, there is no standardised technique for performing or interpreting the manometry test [33]; however, most units have a set of values to reflect their control population and normal values.

The automated pull-through of a multichannel catheter can provide a computerised three-dimensional representation of the pressure profiles[39]. More recently the use of high resolution techniques combined with novel interpretive software has been used to allow the interpolation of manometric recordings into highly detailed topographical plots of intraluminal pressure events relative to time and location [40]. This seems to be well

collaborated with conventional measurements and further studies are being conducted to establish its place in routine physiological assessment.

Clinical value: anal pressures are often reduced in patients with faecal incontinence. Although some studies demonstrate changes in anal pressures in response to different therapies, manometry rarely has prognostic or outcome value. In addition to measuring anal pressures, manometry tests for RAIR and also can demonstrate evidence of paradoxical contraction of the sphincter (dyssynergia) with simulated rectal evacuation[41].

2.8.1.2 RAIR

Reflex relaxation of the upper IAS occurs with progressive rectal filling. Representing the close association between anorectal sensations and motor function, this 'sampling reflex' occurs around every eight to ten minutes allowing rectal contents to be presented to the specialized lower anal sensory epithelium [42]. This process is usually covered by recruitment of the EAS to maintain continence, however, further rectal distension with increasing volumes results in non-recovery of the anal sphincter and imminent defecation. The intactness of the EAS is crucial in resisting the urgency. Contraction of the pelvic floor muscles (puborectalis) allows the return of the rectal contents back to the rectum.

This sampling process allows the sensory anal mucosa to distinguish solids from liquids from gas, an important requirement for maintaining perfect continence[43].

2.8.1.3 Rectal and Anal sensory thresholds

Sensory thresholds include thresholds to distension and to electric stimulation. Rectal distension thresholds can be assessed either by distending a latex rectal balloon manually or by distending a polyethylene rectal balloon using a barostat device[41]. The use of the barostat allows the measurement of both the pressure and the volume of the balloon on distension, therefore permitting assessment of pressure-volume relationships and compliance [44].Anal and rectal thresholds to electric stimulation are assessed using a bipolar electrode catheter.

2.8.2 Structural Assessments

Imaging of the sphincter and the pelvic floor combined with anorectal physiology provides an integrated assessment of sphincter function and aids treatment planning. In this section a brief summary of the most widely used imaging modalities employed. These provide either static anatomical information or more dynamic or functional information.

2.8.2.1 Endoanal ultrasound

Although, transperineal and transvaginal approaches to ultrasonic sphincter imaging are feasible, high resolution scanning using endo-anal probes is the gold standard [45]. Image analysis is usually performed using sequential axial images through the anal canal, although a 3D data volume acquisition is available in certain machines allowing image-analysis in the coronal and sagittal planes.

Endoanal ultrasound gives information about the thickness of the sphincter muscle and the presence of atrophy as well as its integrity and the presence of muscle tearing or injury.

The normal internal sphincter varies in thickness with age, measuring 1-2 mm in young adults and more than 2.8 mm in those older than 55 years of age [46]. Abnormally increased internal sphincter thickness is associated with rectal prolapse and intussusceptions [47]. On the other hand an abnormally thin internal sphincter denotes atrophy and is often seen in passive faecal incontinence. Assessment of atrophy of the external sphincter is more accurate using Magnetic Resonance Imaging (MRI) (see below).

Sphincter injury can be adequately visualised and assessed by endoanal ultrasound. Muscle tears are replaced by fibrous tissue which appears hypo-echogenic on ultrasound [45].

2.8.2.2 Trans-perineal pelvic floor ultrasound

This is both a static and a dynamic study. Although, it is mainly utilised to examine the bladder neck position and motility and to assess rectoceles, ultrasound examination of the sphincter complex can be performed using this method[45, 48].

2.8.2.3 Pelvic floor MRI

High resolution MRI techniques have enabled the detailed examination and delineation of any injury to the muscles of the pelvic floor. The study is performed using a surface coil placed on the pelvis of the patient; however, an endo-coil can be used to obtain detailed images of the sphincter complex (endo-anal MRI).

Endo-anal MRI provides a superior assessment of the sphincter muscle quality[45]. It enables an accurate assessment of degree of atrophy of the external sphincter and any infiltration of its striated muscle fibres with fat cells [49].

2.8.2.4 Dynamic imaging

It is increasingly recognised that often a dysfunction of one pelvic floor compartment is associated with similar dysfunction (potentially less symptomatic) in the other compartments. Dynamic pelvic floor studies allow the global assessment of the pelvic floor to detect abnormalities of structural descent or prolapse or evacuation difficulties.

Dynamic imaging provides functional information on the pelvic floor during a provocatory manoeuvre such as straining, rectal evacuation or pelvic floor contraction [45]. Traditionally, this was limited to the fluoroscopic technique (barium proctography and cysto-proctography); however, with the recent improvement in MRI technology and the development of rapid sequence acquisition, dynamic MRI and MR proctography are increasingly replacing the conventional techniques[45].

2.9 Treatment

There are various modalities and potential interventions within the armamentarium used in treatment of faecal incontinence. Those range from simple interventions to major surgical procedures.

Accurate clinical and physiological assessment of the patient is crucial in informing the process of determination of best treatment options. In my opinion, this is best conducted through a multi-professional approach where the patient's assessment and treatment plan is drawn jointly by professionals who have access and expertise in all available treatment options.

Treatment should - as much as possible - aim to address the underlying pathophysiology and correct the failed component in the continence mechanism rather than follow a rigid step-up algorithm which might not apply uniformly to all presenting individuals.

In this section, I present the various treatment options classified according to their mechanism and target function. The classification also takes into account the invasiveness of the intervention and therefore it represents the escalation in approach to management of FI.

2.9.1 Measures to contain the problem

The use of containement measures such as incontinence pads or anal plugs is potentially a simple way of dealing with symptoms. This can be a definitive intervention in some patients.

2.9.2 Measures to optimise rectal emptying

Optimising and improving rectal emptying can address the problem in a number of patients. Overflow can be a cause of incontinence especially in elderly patients or those with neurological conditions and an empty rectum is less likely to leak.

2.9.2.1 Rectal suppositories or Rectal enemas

2.9.2.2 Rectal irrigation: regular trans-anal rectal irrigation can be a good method of achieving regular effective rectal evacuations with continent intervals between sessions. A number of commercially available systems are present, but patients usually require

training and initial supervision in their use. Complications are rare, but cases of rectal perforation have been reported[50] and this has to be born in mind.

2.9.3 Measures to optimise the utilisation of existing physiological reserves (Biofeedback)

Biofeedback has been defined as 'a form of operant conditioning that can be directed towards pelvic floor retraining, with visual or auditory feedback to encourage sphincter synchrony and strength exercises'[24]. Techniques vary between centres with the common aim being to improve muscular strength and coordination; whilst providing feedback by anal manometry or electromyography.

Norton et al in a systematic review have demonstrated significant results in two thirds of treated patients [51]. The patient-therapist interaction and the presence of motivation and insight on the part of the patient are all crucial elements to the success of this modality [24]. Studies have demonstrated no difference in outcomes between therapy with simple advice and that with invasive feedback techniques [52, 53].

2.9.4 Measures to slow bowel transit and change stool consistency

These are pharmacological agents which slow bowel transit times and subsequently thicken stool consistency. They include the following agents:

1- Loperamide: this is a synthetic opioid which slows gut transit. The availability of a syrup formulation allows fine tuning the dose to avoid constipation[24]. The drug has a safe profile, and tolerance does not seem to develop with chronic administration [24].

2- Opiates: codeine phosphate and other opiate derivatives can be used to slow gut transit, however, tolerance and adverse effects can be problematic.

2.9.5 Neuromodulation

Further details on this modality are discussed in Chapter 3. A number of techniques are performed to induce neuromodulation: Sacral Nerve Stimulation, Pudendal Nerve Stimulation, and Trans-cutaneous or Percutaneous Posterior Tibial Nerve Stimulation. The group of patients who benefit most from this treatment is not determined and positive results have been reported in a wide spectrum of pathophysiologies; however, traditionally this was believed to be most suitable for patients who have functional deficit of the sphincter with integral structure.

2.9.6 Measures to repair/augment the sphincter structure

These are mostly surgical interventions. The long term results of most operations are not always guaranteed and surgery can be associated with significant co-morbidity; therefore, careful counselling of the patients is extremely important.

2.9.6.1 Sphincteroplasty

The commonest cause of sphincter injury is obstetric trauma. If the injury is recognised at the time of delivery a primary end to end or an overlapping repair is performed immediately. However, injuries can be missed and recognised later during the course of assessment during the presentation with faecal incontinence.

In the context of sphincter repair, the first step is to assess the sphincter structurally using endoanal ultrasound or MRI to establish the extent of the injury. The second step is to assess the contractility of the residual EAS as repairing the defect in absence of a contractile EAS will not be associated with improved continence[27]. It is to be noted that an internal sphincter defect can rarely be surgically repaired so in patients with combined IAS and EAS defects the component of passive symptoms persists following surgery [27].

2.9.6.2 Injection of bulking agents

A number of injectables can be used by injection submucosally to create a bulking effect to augment a deficient internal sphincter or by injection to plug isolated defects in the sphincter[54-57]. It appears that the benefit is usually short-lived. The process can also be associated with side-effects (mucosal ulceration, sepsis, agent migration, pain).

2.9.6.3 SECCA procedure

This involves the use of radiofrequency energy delivered to the anal mucosa by special electrodes to create a heating effect that causes tissue fibrosis and scarring[58, 59]. Some studies have demonstrated positive short term clinical outcomes; however, further work is required to establish the long term results and the place of this intervention in the treatment algorithm.

2.9.6.4 Dynamic gracilloplasty

This invasive procedure is usually reserved for those who have an irreparable sphincter and have failed conventional treatments. The operation involves transposition of the gracilis muscle around the anal canal. Conditioning of the muscle with low threshold constant electric stimulation to change type II fast twitch fibres to slow twitch fatigue-resistant fibres is performed using an implanted stimulator. Following 8 weeks of conditioning the patient can control the muscle using an external device to switch the stimulator on and off. The operation is technically challenging and complication rate is high. Complications include infection, displacement of the neurostimulator, anorectal perforation and evacuation difficulties. Multinational data showed that 60% of patients had improved continence and quality of life at two years' post-op [60].

2.9.6.5 Artificial anal sphincter

This is also reserved for severe cases where all less-invasive measures have failed. A number of different designs are available, but the major problem remains the risk of infection. Other potential complications included device malfunction and evacuation difficulties. Revisional surgery is required in almost 50% of patients [61].

2.9.7 Diversion of Stools (Stoma formation)

The formation of a stoma is considered as a last resort for some patients. It is an effective simple measure; however, it has its own physical and emotional impact and long term potential problem including parastomal herniation.

Chapter 3

Neuromodulation for Faecal Incontinence

3.1 Chapter layout

In this chapter I will cover the historical development of Sacral Nerve Stimulation (SNS) as a treatment for faecal incontinence, its techniques and complications and I will present a review of the literature on the current understanding of it mechanisms of action and the physiological changes associated with it.

As will be detailed below, it is currently believed that clinical results achieved with sacral nerve stimulation are results of a neuromodulatory procedure with changes of electrical activity in one neuronal pathway influencing the activity in another. Hence, some authors started to use the term Sacral Neuromodulation when referring to the procedure of Sacral Nerve Stimulation. I have adopted to use the term Sacral Nerve Stimulation in referring to this specific procedure as I believe that Sacral Neuromodulation is a mechanistic term referring to a particular process which can be achieved by stimulation of the sacral nerves (SNS) or indeed other modalities (e.g. Posterior Tibial Nerve Stimulation or by using pharmacological or other means).

3.2 Historical review

The use of electricity in medical therapy is believed to date back to ancient civilisations. Ancient Egyptians are thought to have used electrogenic fish to treat ailments. Scribonius Largus in the first century recorded the first medical use of such fish for the

treatment of pain[62]. Further development in the physics of electricity and its application over the centuries made electrotherapy more popular.

3.2.1 Pain theories and the use of electric stimulation in pain therapy

The application of electrotherapy took off primarily in the field of pain management. Up until the mid twentieth century, the nature of pain was understood through the two controversial theories; the 'specificity theory' which maintains that pain is a specific modality with its own central and peripheral apparatus, and the 'pattern theory' which maintains that the nerve impulse pattern for pain is produced by intense stimulation of non-specific receptors. Melzack and Wall in 1965[63] postulated a new theory of understanding; the 'Gate Control Theory'. In which they proposed that (i) the substantia gelatinosa functions as a gate control system that modulates the afferent patterns before they influence the first central transmission (T) cells, (ii) the afferent patterns in the dorsal column system act as a central control trigger, and (iii) the T cells activate neural mechanism which comprise the action system responsible for response and perception. In effect the theory proposes that pain phenomena are determined by interactions among these three systems[63]. It was later demonstrated that activity in large peripheral sensory nerve fibres carrying non-painful impulses inhibits subsequent activity from small fibres within the spinal cord considered essential to pain conduction[64]. This represented the scientific foundation for the concept of using electric stimulation in pain management.

Smith and co-workers reported establishing anaesthesia and total analgesia in experimental animals using electric stimulation applied to the skull; a concept known as Electronarcosis[65, 66]. However, the first report of application of the stimulating current to the spinal cord was by Shealy et al in 1967 [64]. In an animal experimental study, they reported behavioural as well as electrophysiological changes in 35 cats suggesting suppression of the neuronal pathways activated by noxious stimuli on electric stimulation of the dorsal columns or the anterolateral spinal cord.

The practical use of electric stimulation for pain relief in humans started with application of electric stimulation to peripheral nerves. The prediction based on the 'gate control' theory being that stimulation of large diameter cutaneous afferent nerve fibres might reduce pain. Wall and Sweet[67] reported temporary relief of pain in 8 patients with intense chronic cutaneous pain on electric stimulation (0.1 msec square-waves at 100 cycles/sec for 2 min) of peripheral nerves supplying the painful area. In four patients the relief of pain lasted more than 30 minutes after each stimulation, whilst in the other four it only lasted for few seconds to few minutes after the stimulus ended. They also reported that in two other patients who referred their pain to deep structures rather than to the skin, stimulation of the relevant peripheral nerves failed to alleviate their pain. The authors were quite excited with the results which further elucidated the potential 'gate-control theory' for pain, however they stated that the therapeutic implications are uncertain as the effects in two patients have been found to be gradually decreasing after several months.

The first report of stimulation of the spinal cord in humans was by Shealy et al in 1967[68]. They reported performing a thoracic laminectomy and placing a stimulating electrode close to the dorsal columns at the level of T3 in a patient suffering from chronic severe lower chest and upper abdominal pain attributed to pleural and liver metastases from known inoperable bronchogenic cancer with life expectancy of two months. The symptoms were relieved with stimulation, however, much to the distress of the authors the patient died 48 hours after the operation from undiagnosed subacute bacterial endocarditis and massive cerebral embolism. This case report was followed by other similar reports and Shimogi et al in 1971 reported further analgesic properties of Spinal Cord Stimulation (SCS)[69]. Further research has then demonstrated the efficacy of SCS in providing pain relief in a number of chronic pain disorders relating to diverse aetiology.

It is believed that the effectiveness of SCS is due to several mechanisms[62], including: segmental, antidromic activation restricted to A beta afferents; blocking of transmission in the spinothalamic tract; supra-spinal inhibition; and activation of putative neurotransmitters or neuromodulators.

3.2.2 The use of electric stimulation in bladder disorders

On another front, the use of electric stimulation to induce bladder emptying was being tried for a long time as an idea to manage the neurogenic bladder in patients with spinal cord injury. Since Budge in 1864 who tried stimulating the pelvic nerves[70], a number of

investigators have attempted electric stimulation of the bladder targeting the detrusor muscle, the pelvic nerves or the pudendal nerve. The results were not particularly successful as mostly stimulation was associated with pain; the main reason being the failure to locate a trigger point which can effectively stimulate bladder contraction without the diffusion of stimulation to pelvic muscles and nerve plexi. Habib in 1967[71] concluded – following his experimental work carried out on 64 dogs and 5 paraplegic patients since 1962 – that a better approach would be to stimulate the sacral nerve roots. He documented poor outcomes in two patients who underwent direct myogenic stimulation, compared to good results in those who underwent stimulation of the third and fourth sacral nerve roots. Although the surgical approach to the sacral nerves he described was an anterior trans-abdominal approach, he suggested that a posterior parasacral approach will be easier and associated with fewer complications.

Animal and cadaveric studies by Tanagho and Schmidt[72, 73] concluded the feasibility of inducing bladder emptying by electric stimulation of the anterior motor sacral roots selectively. This was developed clinically and the effective application by Brindley using high-voltage stimulation of the anterior sacral roots (accompanied with dorsal rhizotomy) allowed patients with spinal cord injury to achieve intermittent complete bladder emptying[74].

The work of urologists on the neurogenic bladder yielded several observations from the evaluation, implantation and follow up of these patients. They noticed that voiding is only produced when sphincter resistance is greatly minimized (with pudendal nerve

blocks and subsequent selective neurotomies)[75]. They also observed that the bladder responses were better after than before pudendal nerve block. This observation suggested that sphincteric stimulation inhibits bladder contraction and the concept that enhancing tone within the external urethral sphincter with electric stimulation will have a suppressive effect on the detrusor and improve storage was developed[75].

This formed the basis for using SNS in patients rendered incontinent because of detrusor overactivity or in patients with other categories of bladder dysfunction with good clinical outcomes.

As part of the application of SNS in urological dysfunction, some patients reported the additional associated improvement of their bowel function and rectal evacuation suggesting an associated effect on the anorectum[74].

3.2.3 The use of SNS in faecal incontinence

Matzel et al in 1995[76] reported the first use of SNS techniques in the treatment of faecal incontinence. Significant improvement of symptoms in 3 patients with faecal incontinence secondary to functional sphincteric deficit (with intact structure) was reported with six months follow up.

Since this report a number of studies stated similarly positive results in patients with faecal incontinence of mixed aetiologies in the presence of structurally intact anal

sphincters[77-80]. Furthermore reports of positive results in patients with scleroderma[81] and incontinence following radiotherapy and anterior resection[82] were also published. Furthermore, some studies have demonstrated a positive clinical outcome using this modality in patients with persistent external sphincter defects[83-85].

Multiple series reporting positive outcomes formed the evidence base for the National Institute for Clinical Excellence (NICE) to issue its guidance in November 2004[86] supporting the use of this procedure for treatment of faecal incontinence in specialised centres. The clinical outcomes are discussed in detail in section 3.3 within this chapter.

3.2.4 The use of SNS in constipation

More recently, SNS has been used to treat constipation. The effect of sacral root stimulation on bowel motility was established when direct stimulation of the anterior sacral nerve roots in patients with spinal cord injury was found to be associated with the induction of peristaltic colonic activity associated with bowel evacuation[74, 87].

The effect of temporary SNS on idiopathic constipation was later studied; Ganio et al[78] reported the results of temporary stimulation in 10 patients identifying a subjective improvement in defecation but with no increase in frequency. Malouf et al[88] reported significant clinical improvement including increased frequency of evacuation in 2 out of 8 patients following 3 weeks of stimulation. Kenefick et al[89] reported similar results in 4 patients who went on to have permanent implants.

3.3 Review of the evidence in faecal incontinence

Most of the clinical evidence regarding efficacy of SNS in faecal incontinence is constituted of case series. Those are mostly of only short to mid-term follow up data. Only few studies have involved randomization. I identified only three cross-over studies and a single blinded randomized trial. This is in agreement with the findings of the short version Cochrane Review conducted by Mowatt et al[90].

3.3.1 Case series

Since the initial report by Matzel et al in 1995[76], numerous reports of improvement of faecal incontinence with SNS have emerged. Those can be grouped as follows according to the recruited patients and the aetiology of faecal incontinence:

3.3.1.1 Patients with intact target organ and preserved nerve supply

Patients with functionally defective but structurally integral sphincters represented the first group of patients in which SNS was applied. Patients were usually selected for SNS if they had a structurally intact External Anal Sphincter (EAS) with preserved neuromuscular connections (evidenced by the ability to generate a voluntary anal squeeze and the presence of a response on testing of pudendal nerve latency). Most reports were single-centre studies[76, 77, 79, 91] and the number of patients ranged from 3 to

23. However, some multi-center studies were also carried out, albeit with small number of patients. Matzel et al reported results of 37 patients from 8 centres in 2004[80].

Most studies had short term follow up, however, Melenhorst et al in an important study reported 5 years' follow up data for 100 patients with permanent implants[92].

Within this category (patients with structurally intact external sphincter), some studies have reported positive results in certain special indications. For instance a number of preliminary studies reported good results following rectosigmoid resections for cancer[82, 93-95]. Additionally, a study of results in five patients with incontinence associated with Scleroderma reported good results in four of them in 2002[81].

3.3.1.2 Patients with disrupted EAS

It was logical to initially restrict the use of SNS to patients with a structurally intact EAS, as although its mechanisms of action were not fully understood, it was thought that its efficacy is based on restoring normal sphincter function and so an intact target organ was a requirement. However, a preliminary report of five patients suggested that SNS may successfully restore continence in some patients with sonographic evidence of an EAS defect[83]. Jarrett et al also reported good results in 5 out of 8 patients with sonographic evidence of EAS disruption (more than 30 degrees)[84].

Moreover, Chan et al conducted a prospective comparison between clinical outcomes of SNS in patients with and without sonographic evidence of EAS disruption, reporting that both groups responded in the same manner with no statistical difference in outcomes after PNE, at 3months and 6months post SNS[85]. Nevertheless, the authors reported that there was a trend towards poorer bowel diary variables in the group with EAS disruption as shown by a higher number of incontinent episodes and usage of pads.

Although these reports mostly included small numbers, the feeling among experts is that SNS results in this group of patients seem to be similar to those with an intact sphincter[96].

Some have even claimed that SNS could represent a valid management option instead of surgical repair in treating fresh obstetric injuries. However, caution should be exercised in this context as there is no long term follow up data in this group; additionally the studies mentioned above present findings in patients within the middle age group with the majority of them having had a surgical sphincter repair. Moreover, this makes the diagnosis of sphincter disruption based on sonographic findings in these patients open to different radiological interpretation and debate.

3.3.1.3 Neurogenic incontinence

Some studies have demonstrated that SNS can be associated with an improvement of neurogenic faecal incontinence[97-101]. Patients in these studies included mainly

incomplete medullary or cauda equina lesions (traumatic or vascular lesions, spina bifida or multiple sclerosis). Follow up data is still limited but this is certainly a promising application.

Nevertheless, experts call for careful evaluation when considering this application in patients with progressive neurological conditions as Multiple Sclerosis as the progression of illness could lead to rapid secondary failure of SNS and also the presence of the SNS device can impede the often needed monitoring and diagnostic MRI[96].

3.3.2 Randomized studies

3.3.2.1 Randomized cross-over studies

Only two studies conducted a randomized cross-over in patients treated with SNS for FI. Vaizey et al [102] enrolled two patients who have been implanted with SNS devices for 9 months. The cross-over trial involved alternating two-week periods with the device ON and OFF and the results reported were indicative of significant improvement of symptoms when the device was ON. Although authors state the methodology was blinding to both the patient and the investigator, it is to be highlighted that even with sub-threshold stimulation blinding of the patient can be challenging.

In a multi-centre study, Leroi et al[103] enrolled 27 patients after their permanent implantation into a double-blinded cross-over trial where patients were randomized to

one month period of ON and OFF in a cross-over fashion with no washout period. Authors reported significant treatment effect with a decrease in median frequency of FI episodes between stimulation ON and OFF. Interestingly, despite more marked improvement in symptoms during the ON period, patients also seem to have improved during the OFF period leading to the suggestion of a potential placebo effect. Also, they reported that at the end of the cross-over study 18 patients expressed a preference for the stimulation ON, whereas 6 preferred stimulation OFF and 3 had no preference.

3.3.2.2 Randomized trial comparing SNS to conventional therapy

Only a single study conducted a randomized trial comparing outcomes of SNS to those of maximal medical therapy. Tjandra et al randomized around 60 patients to each group and found significantly better results in the SNS group with 12 months' follow up[104]. The study was well designed, however, it is to be stated that patient blindness is impossible in such design. Moreover, the study was set to compare a state-of-the-art intervention with basic supportive conservative therapy and therefore it has an inherent risk for bias by unblinded patients or practitioners.

3.4 SNS in clinical practice

Patients chosen for this treatment are usually those with refractory incontinence which has failed conservative medical therapies. The clinical response is first assessed during a trial period using an external nerve stimulator (temporary SNS) prior to the surgical

implantation of the Interstim neuro-stimulator. A temporary wire is usually used during the trial stimulation phase; however some surgeons use the permanent quadripolar tined lead for temporary stimulation.

Most centres select patients for permanent implantation if their reported clinical response showed an improvement of incontinence of 50% or more (based on completion of detailed bowel diaries). Studies also occasionally report quality of life data[80, 105].

3.4.1 Success rates

A systematic review reporting results of six studies published in the period from 2001-2004 involving 266 patients reported that 56% of the patients proceeded to permanent implantation[105].

Table 3.1 below summarizes the outcomes in SNS case series. The collective average success rate of temporary stimulation is around 79% (251 patients from the total of 329), however, the number of patients proceeded to permanent implantation is slightly smaller secondary to usually the timing of results' publication.

Table 3.1 Clinical outcomes in case series of permanent SNS implants:

	Matzel 1995 [76]	Ganio 2001 [79]	Rosen 2001	Leroi 2001 [91]	Matzel 2004 [80]	Uludag 2004 [106]	Altomare 2004 [98]	Melenhorst 2007 [92]	Gourcerol 2007 [107]	Tjandra 2008 [104]
Temporary SNS (n)	3	19	Intraop testing only	9	37	75	-	134	61	59
Success rate of temporary	3 (100%)	17 (89.5%)	-	8 (89%)	34 (92%)	62(83%)	-	100 (75%)	35 (57%)	54 (92%)
Permanent implants	3	5	16	6	34	50	14	100	33	53
Success at 3months	-	-	16 (100%)	5 (83%)	34 (100%)	-	-	-	-	-
Success at 6months	3 (100%)	5 (100%)	-	3 (50%)	34 (100%)	-	-	-	20/29 (69%) note 4 lost to follow up	-
Success at 12months	-	5 (100%)	-	-	34 (100%)	48 (96%)	14 (100%)	-	16/20 (80%) note 13 lost to follow up	38 (72%)
Success at 50months	-	-	-	-	-	-	-	79 (79%)	-	-

3.4.2 Reproducibility of therapeutic effects observed during the screening phase

Several studies show that there is a degree of loss of efficacy of stimulation with time. Around 20 to 30% of patients who had responded to temporary stimulation and received a permanent implant loose the clinical benefit within a year.

Melenhorst et al[92] in a report of 5 years' follow up of 100 permanent implantations mentioned that 21 patients lost the beneficial clinical effect of stimulation after a median of 1 year from implantation. Roman et al[108] also showed that only 14 out of the 18 patients who proceeded to permanent implantation had a significant improvement of their symptoms at 3 months follow up. In addition to a high proportion of patients lost to follow up, Gourcerol et al[107] reported similar results.

The reasons behind this phenomenon are not understood. An over-rated initial response reported by patients following temporary stimulation is a possible reason. Some have suggested that the use of the quadripolar lead during the trial stimulation might be associated with increased positive outcomes with stimulation[109, 110], however, others demonstrated that this is not necessarily the case[107].

3.5 Suggested mechanisms of action and the observed physiological changes

Despite a reasonably established body of clinical evidence, the underlying mechanisms of action and physiological pathways are not fully understood yet. A number of studies have examined the potential physiological changes with SNS, however findings have been inconsistent.

3.5.1 Anal pressures

It is interesting that the effect of sacral nerve stimulation on anal pressures has not been consistent in various studies. It would have been intuitive that the stimulation would lead to increased pressures secondary to external sphincter contraction.

The motor response which is observed to check the correct placement of the leads intra-operatively includes the typical anal wink and bellows action, however this is usually elicited under general anaesthetic and the threshold used for stimulation afterwards is much lower and hence could potentially explain the absence of evidence of increased anal pressures with stimulation in some reports.

The observed motor response on testing intra-operatively most likely includes a component of pelvic floor contraction. Matzel et al[111]in an experimental study examined the effect of electrically stimulating the S3 nerve showing that this leads to a decrease in

the rectoanal angulation (demonstrated by fluoroscopy with a contrast filled Folley's catheter in the rectum) with only a slight increase in the anal pressure (measured with anal manometry), however, stimulation of the pudendal nerve was associated with significant increase in anal pressures. His human cadaveric dissection, demonstrated that the nerve supply to levator ani and the external sphincter is derived from a common source (roots S2 to S4), however those to the levator ani are direct branches splitting from the sacral nerves proximal to the sacral plexus whilst those to the external sphincter are nerve fibres running with the pudendal nerve[111]. In this context, it should be highlighted that anal manometry reflects only the sphincteric pressures when in actual fact significant changes occur also at the level of the levator ani and with the rectoanal angle. Another variable in the equation here is the time factor. Effects of subacute and chronic stimulation might vary significantly from those of acute stimulation seen during wire insertion in the operating room.

The initial understanding of the process of SNS was that it aims to increase the anal canal closure pressure through the resulting contraction of the pelvic floor and sphincter muscles leading to direct improvement of continence abilities. It was believed that the increase in the voluntary sphincter function could be related to a permanent training effect of the muscle itself; with stimulation-induced transformation of fast twitch fatiguable muscle fibres (type II) to slow twitch fatigue-resistant fibres (type I)[76, 112]. However, authors soon started to think that the effects of stimulation are likely to be more diverse than a simple effect on the efferent motor supply to the sphincter[77].

Fowler et al[113] conducted a study on 9 patients (spinally intact) whilst having temporary SNS wires inserted measuring the latency of the response of the striated external anal sphincter following sacral nerve stimulation. The findings were very interesting, as the mean latency of the response was 98 milliseconds which is ten times longer than would be expected if the response was a result of direct motor nerve stimulation. All patients in this study had urological indications for the procedure with fully intact anorectal units. It was rather interesting to note that the patient in whom the PNE did not have a clinical effect had the shortest latency. The authors concluded that this relative extreme prolongation of the latency of the anal sphincter response following S3 foramen stimulation indicates that the response is reflexly induced afferent-mediated. Moreover, they stated that the picture of the response was consistent with mediation through a polysynaptic reflex.

Further to Fowler's work, Schurch et al[114] studied anal electromyographic responses to S3 stimulation in 3 patients with complete spinal cord injury in an attempt to establish whether the reflex response originates from a segmental level within the sacral spinal cord or from supraspinal neuronal centres involving the spino-bulbo-spinal pathways. They observed at least two reproducible electromyographic responses after direct stimulation of S3. The early response appeared with a mean latency of 41.2 msec corresponding to the segmental pudendo-anal reflex. The second response appeared variable in onset with minimum latency of mean 189.4 msec suggesting a polysynaptic afferent-mediated reflex response. Authors suggested that recording such a late response in patients with complete spinal cord injury in whom all spino-bulbo-spinal loops are

supposed to be interrupted suggests that it is of spinal origin. However, as none of the patients in the study developed a clinical response to continuous stimulation for 5 days, they suggested that an intact spino-bulbo-spinal pathway (although appears unnecessary for eliciting the electromyographic anal response) might be necessary in establishing the clinical response to neuromodulation.

In respect of manometry-determined anal pressures, studies have shown variable findings. Some studies have demonstrated an increase in the squeeze pressures with temporary and permanent stimulation, but effects on the resting pressure were less consistent (see table 3.2).

Matzel et al[76] in the initial report of SNS in faecal incontinence showed serial increases in the maximum squeeze pressure during PNE and following permanent implantation up to the last measurements made 24 months post-operatively in 3 patients who reported a good clinical result with the stimulation.

Vaizey et al[77] reported similar findings in the report of results of SNS in 12 patients (physiological results for 9 patients only as wire dislodgement in 3) with mixed aetiology of FI but all with no sphincteric defects. They similarly reported an increase in squeeze pressure 24 hrs and few weeks following PNE with no change in resting pressures; however a qualitative change in the form of reduction of the number of rectal motor complexes and dips in anal pressures was suggested from the analysis of 24 hours' ambulatory anorectal manometry of unprepared bowel in 9 patients. The same

group in a small cross-over study in two patients with permanent implants showed that these changes are reversed with the switching OFF of the device[102].

Rosen et al[97] reported positive clinical results in 16 patients with faecal incontinence (neurological and idiopathic aetiology) who underwent permanent implantation following a good motor response to test stimulation intraoperatively. Clinical results were associated with significant increase in the resting and squeeze anal pressures on assessment 3 months post-operatively.

Leroi et al[91] reported results of temporary stimulation in 9 patients with faecal incontinence of mixed aetiology including some patients with small sphincteric defects on EAUS. Eight of the patients responded well to temporary stimulation and six of which proceeded to permanent implantation at the time of reporting. Physiological assessment in this group of patients revealed no change in resting pressure but increased maximal squeeze pressure during temporary stimulation in comparison with pre-stimulation. Manometry at 3 months following implantations revealed no change in either resting or squeeze pressure amplitudes but significant increase in duration of voluntary contraction. Authors mentioned that this observed increase in duration of contraction associated with no or occasional decrease in amplitude could be because of a change in muscle phenotype.

In a study of the effects of magnetic sacral nerve stimulation (MSNS) which involves using a magnetic coil placed over the sacral region inducing an electric field which

stimulates the sacral nerves (Faraday's Law), Morren et al[115] examined 14 healthy controls, 18 patients with faecal incontinence and 14 patients with spinal cord injury (SCI) (3 complete cervical, 7 complete thoracic, 3 incomplete cervical, 1 incomplete thoracic). They reported an alteration of anal pressures with stimulation in 39 out of the 46 subjects. Pressures increased at three levels (proximal, mid and distal) in the anal canal with stimulation, but in two SCI patients and one control subject a drop instead of rise was seen in the mid-canal. In more than quarter of the FI patients no rise of anal pressures could be evoked with stimulation, with no relation between this and the presence of pudendal neuropathy or sphincter defects in this cohort. Authors indicated no such failure in the control group, indicating that the stimulation technique itself is not the limiting factor.

Kenefick et al[81] in a series of the results of temporary and permanent stimulation in 4 patients with faecal incontinence secondary to scleroderma with evidence of IAS atrophy on EAUS reported that maximal resting and squeeze pressures increased following stimulation. In a report of larger cohort of patients (19patients) with various aetiology of incontinence[116], the same author reported a significant increase in maximal squeeze pressure with stimulation.

On the contrary to Kenefick et al[89] who reported the results of stimulation in 4 patients with constipation stating a trend towards an increase in the resting and maximal squeeze pressure, Malouf et al[88] in the report of results of temporary SNS used in 8 patients with constipation reported no significant change in anal pressures with the stimulation.

Jarrett et al[117] reported results of multicentre experience in the UK (three centres: 59 patients with 46 proceeding to permanent implantation). The reported anorectal physiological results comparing baseline measurements versus measurements after permanent stimulation included a significant increase of the maximal squeeze pressure with no change in maximum resting pressure.

Uludag et al[106] showed no significant change in neither resting nor squeeze pressure with chronic stimulation in 50 patients who underwent permanent implantation with manometry follow up at 1, 3, 6, 12 and 24 months. Similarly Altomare et al[98] showed no change in the resting or squeeze pressures in 14 patients who underwent permanent implantation.

In a series of 12 patients with partial spinal injury and faecal incontinence who underwent permanent SNS implantation, Jarrett et al[99] reported that no changes were seen in resting or squeeze pressure at 1, 3, 6 and 12 months post-implantation.

Ratto et al[82] reported positive clinical results in 4 patients with FI associated with Neoadjuvant radiotherapy and Anterior Resection for rectal cancer who were treated with permanent SNS implants. Authors reported some manometric changes and changes in rectal sensitivity with the stimulation, and although changes were inconsistent amongst the four patients they stated that it followed the clinical results. Although the numbers are very small and no real extrapolation can be made from this study, it is to be said that mechanisms and pathways underlying such potential changes will be very

difficult to explain as the autonomic plexi are usually disturbed with the mesorectal excision. Another important point here is the fact that such patients with an underlying malignant disease which might necessitate the investigation with magnetic resonance imaging to check for the potentiality of a post-operative recurrence are not the ideal candidates for SNS implants.

Michelsen et al[118] in a study of physiological changes pre- and 6 months post-permanent implantation in 29 patients with faecal incontinence (only one patient with partial cauda equine lesion) demonstrated that resting and squeeze pressures increased (albeit not to statistical significance in the case of the squeeze pressures).

Melenhorst et al[92] reported a significant increase in the squeeze pressures at 6, 12 and 24 months following chronic stimulation but this was associated with no significant change in the resting pressures.

In a comprehensive review on the subject, Carrington et al [119] concluded that to date, conflicting data exist on the mechanisms of action of SNS as determined by end-organ changes in anorectal physiology. In a table (presented as Figure 3.1 below), the authors demonstrated the lack of evidence of a consistent change in anal pressures with SNS.

Author [reference no.]	Year	n	Temp/ Perm	Anal resting pressure cm H_2O			Max squeeze pressure cm H_2O		
				Pre SNS	Post SNS	*P* value	Pre SNS	Post SNS	*P* value
Vaizey *et al.* [32]	1999	10	Temp	40 (25–140)	57 (20–95)	nr	33 (10–120)	75 (25–165)	nr
Malouf *et al.* [33]	2000	5	Perm	40 (16–40)	49 (32–90)	ns	80 (10–140)	81 (30–187)	ns
Ganio *et al.* [21]	2001	40	Temp	39 (7)	54 (8)	0.01	85 (9)	99 (1)	0.047
Rosen *et al.* [22]	2001	16	Perm	28 (16–39)	50 (29–76)	0.005	59 (28–87)	120 (57–193)	0.005
Ripetti *et al.* [23]	2002	9	Temp	59 (16)	74 (11)	0.0001	89 (36)	110 (28)	0.003
Kenefick *et al.* [34]	2002	4	Perm	37 (16–39)	65 (47–85)	nr	89 (40–120)	105 (43–204)	nr
Matzel *et al.* [35]	2002	1	Perm	43	50	nr	75	115	nr
Altomare *et al.* [36]	2003	14	Perm	'No change'		nr	'No change'		nr
Buntzen *et al.* [37]	2004	1	Perm	38	67	nr	38 (nr)	82	nr
Rasmussen *et al.* [38]	2004	43	Perm	42 (20–112)	33 (12–106)	ns	90 (44–160)	100(42–151)	ns
Uludag *et al.* [39]	2004	75	Perm	'No change'		nr	'No change'		nr
Jarrett *et al.* [14]	2004	46	Perm	46 (23)	49 (24)	ns	62 (53)	93 (47)	0.007
Sheldon *et al.* [2]	2005	10	Temp	66 (9)	67 (12)	nr	58 (20)	55 (20)	nr
Koch *et al.* [40]	2005	8	Perm	'No change'		nr	'No change'		nr
Uludag *et al.* [41]	2006	14	Perm	39 (nr)	48 (nr)	ns	66 (nr)	71 (nr)	ns
Michelsen *et al.* [5]	2006	29	Perm	31 (0–109)	38 (0–111)	0.045	51 (0–127)	54 (0–118)	ns
Kenefick [16]	2006	19	Perm	nr	nr	nr	27 (5–140)	55 (7–204)	nr
Holzer *et al.* [24]	2007	29	Perm	44 (15–87)	60 (21–112)	0.001	56 (0–104)	95 (25–120)	0.001
Melenhorst *et al.* [11]	2007	100	Perm	'No change'		nr	'Significantly higher'		0.007
Munoz-Dyos *et al.* [42]	2008	57	Perm	45 (5–102)	41 (28–56)	nr	79 (17–192)	91 (41–166)	ns
Jarrett *et al.* [43]	2008	8	Perm	34 (23–50)	31 (5–64)	nr	14 (10–56)	31 (19–87)	ns
Holzer *et al.* [44]	2008	7	Perm	44 (20–92)	48 (30–89)	nr	72 (37–112)	79 (42–125)	
Altomere *et al.* [13]	2009	65	Perm	'Significantly higher'		0.003	'Significantly higher'		0.001
Dudding *et al.* [45]	2010	9	Perm	38 (16–47)	41 (33–81)	nr	90 (55–199)	81 (55–106)	ns
Koch *et al.* [46]	2010	19	Perm	55 (20)	67 (25)	nr	81 (34)	111 (58)	ns
Michelsen *et al.* [47]	2010	142	Perm	33 (0–119)	37(0–141)	ns	49 (0–122)	52.5 (0–165)	ns
Uludag *et al.* [48]	2010	12	Perm	46 (nr)	50 (nr)	nr	67 (nr)	72 (nr)	nr

Values are median (range) or mean (SD), as described by the authors, and expressed as cm H_2O; shaded values were expressed as statistically significant increases from baseline; descriptions in inverted commas represent quotes from the text when no absolute data were provided.

Temp, temporary change; perm, permanent change; nr, not reported; ns, reported as not significant.

Figure 3.1 – Findings of studies examining anal resting and squeeze pressures before and after SNS (From Carrington et al [119] with permission)

Table 3.2: Anal manometry findings in studies of SNS for faecal incontinence:

Study	**Indication**	**Pts**	**Structural integrity of external sphincters (no. of pts)**	**Technique of SNS**	**Technique of manometry**	**Resting**	**Resting**	**Resting**	**Squeeze**	**Squeeze**	**Squeeze**
						Post PNE	**3 months**	**6 months**	**Post PNE**	**3 months**	**6 months**
Matzel 1995 [76]	- Functional	3	- Intact (2) - Previous repair (1)	Trans-foraminal	Not mentioned	No change	No change	No change	Increased	Increased	increased
Vaizey 1999 [77]	- Functional	9	- Intact (9)	Trans-foraminal		No change	-	-	Increased	-	-
Ganio 2001 [79]	- Functional - Neurological	19	- Intact (19)	Trans-foraminal	Not mentioned	Increased	-	-	Increased	-	-
Rosen 2001 [97]	- Neurological - Idiopathic	16	- Intact (16)	Trans-foraminal	Not mentioned	-	Increased	-	-	Increased	-
Kenefick 2002 (scleroderma) [81]	- Scleroderma	4		Trans-foraminal	Stationary pull thru (8 channel water perfused) - squeeze meant maximum increment above resting	Increased	-	-	Increased	-	-
Leroi 2001 [91]	- Obstetric - Post-operative - Neurological - Idiopathic	9	- small sphincter defects (4)	Trans-foraminal	See ref 10 & 11 of the paper	During PNE: no change	No change	No change	During PNE: increased	No change (but duration of squeeze increased)	No change
Jarret 2004 [117]	- Obstetric - Post-operative - Scleroderma - Idiopathic - Spinal trauma	46	- defect (4) - atrophy (4) - previous overlapping repair (10)	Trans-foraminal	Stationary pull thru (8 channel water perfused)	-	No change	-	-	Increased	-

Study	**Indication**	**Pts**	**Structural integrity of external sphincters (no. of pts)**	**Technique of SNS**	**Technique of manometry**	**Resting**	**Resting**	**Resting**	**Squeeze**	**Squeeze**	**Squeeze**
						Post PNE	**3 months**	**6 months**	**Post PNE**	**3 months**	**6 months**
Uludag 2004 [106]	- Idiopathic - Partial SCI or slipped disc - Previous sphincter repair - Post-operative	52	All intact	Trans-foraminal	Solid state catheter (Konisgsberg catheter)	-	No change	No change	-	No change	No change
Altomare 2004[98]	- Neurogenic - Sacral trauma or surgery - Post-operative - Anorectal malformation	14	Not reported	Trans-foraminal	No mentioned-	-	No change	-	-	No change	-
Jarrett 2005 [99]	- Partial Spinal Cord Injury	12	- intact (11) - previous repair (1)	Trans-foraminal	Station pull through	-	No change	No change	-	No change	No change
Uludag 2005 [120]	- partial spinal cord injury in one pt	15	- intact (13) - previous repair (2)	Trans-foraminal	Konigsberg catheter	No change	-	-	No change	-	-
Michelsen 2006[118]	- idiopathic - sphincter defects - anorectal surgery - rectal resection - rectal prolapse - diabetic - incomplete cauda equina lesion	29	- intact (24) - sphincter defects (5)	Trans-foraminal	-	-	-	Increased	-	-	Increased (but not to statistical significance)

Study	**Indication**	**Pts**	**Structural integrity of external sphincters (no. of pts)**	**Technique of SNS**	**Technique of manometry**	**Resting**	**Resting**	**Resting**	**Squeeze**	**Squeeze**	**Squeeze**
						Post PNE	**3 months**	**6 months**	**Post PNE**	**3 months**	**6 months**
Kenefick 2006 [116]	- Scleroderma - Obstetric injury - Idiopathic - Post anorectal surgery - Partial SCI T2/3 (1case only)	19	No information	Trans-foraminal	-	-	-	-	Increased	Increased	Increased
Melenhorst 2007[92]	- Idiopathic - Obstetric injury - Anal repair - Neurogenic (Note neurologic disease, MS and diabetic neuropathy were excluded)	100	All had intact sphincters (but some had previous repairs)	Trans-foraminal	Konigsberg catheter	-	No change	No change	-	No change	Increased (also at 12 and 24 months)

3.5.2 Recto-Anal Inhibitory Reflex (RAIR)

RAIR is an important component of the continence mechanism (see chapter 2). Only two studies have examined the RAIR parameters when studying potential anorectal physiological changes with SNS. Ganio et al reported no demonstrable change in 19 patients [79]. Altomare et al showed no change in the latency or duration of the reflex but noted a slight reduction of the volume threshold at which the reflex is elicited [98].

3.5.3 Saline retention test

Saline retention time was measured by some investigators examining the effects of SNS in faecal incontinence. Matzel et al in the first report of this treatment showed [76] an increase in all three patients when tested few weeks following stimulation. Other authors showed similar results [91, 97].

3.5.4 Rectal distension thresholds

3.5.4.1. Balloon studies

Assessment of rectal sensory function following SNS revealed conflicting evidence. Vaizey et al[77] showed an increase in all thresholds with rapid balloon distension, however, there was no change with slow water infusion.

Ganio et al[79] showed a decrease in the pressures associated with First Sensation (FS) and Urge (U) sensation, however only the volumes associated with Urge sensation were significantly reduced following stimulation. Other authors reported reduction of the urge volumes [91] or all rectal threshold volumes with stimulation [81, 97, 117].In a large study of 100 patients who underwent permanent implantation for FI, Melenhorst et al[92] reported no significant change in the rectal threshold volumes following a year of stimulation. Kenefick[116] reported a significant reduction of the First threshold and Maximum Tolerated Volume with stimulation in a study of 19 patients with FI who underwent physiological testing pre- and post- temporary SNS as well as 3,6 and 12 months post implantation.

3.5.4.2 Barostat Studies

Uludag et al[120] utilized the barostat device to study rectal thresholds in 15 patients before and at the end of the screening period of temporary SNS. Patients were asked to report rectal filling sensations: First Sensation (FS), Earliest Urge to Defaecate (EUD) and an irresistible urge to defaecate (Maximum Tolerated Volume) using isobaric phasic distension. Authors reported that the median volume thresholds for FS, EUD and MTV decreased significantly with the stimulation. Interestingly this was also associated with significant reduction of the calculated rectal wall tension for each sensory threshold. The pressure thresholds tended to decrease but a significant reduction was noticed only for the pressure required to evoke the MTV. Roman et al[108] used similar barostat protocol to assess rectal functions after 3 months of chronic stimulation in 18 patients who were

implanted for FI (mainly of idiopathic and obstetric aetiology). They demonstrated no significant change in any of the rectal sensory thresholds with the stimulation.

We ought to be careful when correlating physiological changes with clinical results and in trying to interpret the data and understand the mechanisms of action. Ratto et al[82] as mentioned above have reported some changes in the neorectal sensory thresholds in 4 patients who underwent permanent SNS implantation for the treatment of FI following anterior resection and neoadjuvant radiotherapy for rectal cancer. Although, the number of patients in the study was very small and the findings were inconsistent between patients, authors concluded that SNS was effective in normalizing the neorectal sensory thresholds; inducing an increase in the thresholds in those with normal or low baseline values and a decrease in the thresholds in those with baseline values exceeding normal limits. They extrapolated that those who don't follow this pattern have less favourable clinical response. Let alone the fact that the number of the patients are very small to come up with these conclusions, interpreting this physiologically would be challenging especially in patients who most likely have disrupted autonomic plexi following anterior resection.

Michelsen et al[118] reported completely different findings in a study of the physiological changes pre- and six months post- permanent stimulation in 29 patients. They reported that the median threshold for all sensations (FS, Desire To Defaecate and MTV) had increased with stimulation. In their study of the rectal wall properties, they reported that rectal volumes at each distension pressure (using distension pressures of 0, 5, 10, 15, 20

and 25 cmH2O) was higher at six months, however, the slope of the rectal pressure-volume curves and thereby rectal volumes were largely unchanged. They concluded that the increased volumes and sensory thresholds indicate that SNS caused some rectal relaxation without significantly changing the visco-elastic properties of the rectal wall. This could only be potentially explained through a neuromodulatory effect, but it is at complete odds with most studies which show reduced sensory thresholds with stimulation. Despite that we believe that effects are possibly through an afferent-mediated response, it is well understood that eventual stimulation of parasympathetic pathways to the rectum usually lead to a stimulatory motor response.

Table 3.3: Summary of changes in rectal sensory thresholds in studies of SNS for FI

Study	Indication	Pts	Structural integrity of external sphincters (no. of pts)	First Sensation	Urge	Maximum Tolerated Volume
Vaizey 1999[77]	- Functional	9	- Intact (9)	Increased	Increased	Increased
Ganio 2001[79]	- Functional - Neurological	19	- Intact (19)	No change	Decreased	No change (but tendency fro Increase)
Rosen 2001[97]	- Neurological - Idiopathic	16	- Intact (16)	Decreased	Decreased	Decreased
Leroi 2001[91]	- Obstetric - Post-operative - Neurological - Idiopathic	9	- small sphincter defects (4)	No change	Decreased	No change
Kenefick 2002 (scleroderma)[81]	- Scleroderma	4		Decreased	Decreased	Decreased
Jarret 2004[117]	- Obstetric - Post-operative - Scleroderma - Idiopathic - Spinal trauma		- defect (4) - atrophy (4) - previous overlapping repair (10)	Decreased	Decreased	Decreased
Altomare 2004[98]	- Neurogenic - Sacral trauma or surgery - Post-operative - Anorectal malformation	14	Not reported	No change	No change	No change
Uludag 2005[120]	- partial spinal cord injury in one pt	15	- intact (13) - previous repair (2)	Decreased	Decreased	Decreased
Michelsen 2006[118]	- idiopathic - sphincter defects - anorectal surgery - rectal resection - rectal prolapse - diabetic - incomplete cauda equina lesion	29	- intact (24) - defects (5)	Increased (but no statistical significance)	Increased	Increased
Kenefick 2006[116]	- Scleroderma - Obstetric injury - Idiopathic - Post anorectal surgery - Partial SCI T2/3 (1case only)	19	-	Decreased	-	Decreased

Melenhorst 2007[92]	- Idiopathic - Obstetric injury - Anal repair - Neurogenic (Note neurologic disease, MS and diabetic neuropathy were excluded)	100	All had intact sphincters (but some had previous repairs)	No change	No change	No change
Roman 2008[108]	- idiopathic - obstetric - post-hysterectomy - post anal fistula - neurologic	18	Sphincter defect in 3 pts	No change	No change	No change

3.5.5 Rectal compliance

Rectal compliance is an important measurement of rectal distensibility; a property which is crucial to the rectum as a 'reservoir'. Seven studies have examined the effect of SNS on this aspect of rectal physiology. Most studies that have attempted to examine this rectal property used methods that were far from accurate. Only three studies have utilized the electronic Barostat device which facilitates accurate measurements of rectal wall properties[108, 118, 120].

3.5.5.1 Non-barostat studies

Vaizey et al [77] reported an increase in rectal compliance after 24 hours of stimulation, with compliance returning to the baseline level after 7 days of stimulation. Others reported no change [91] or an increase with stimulation [79].

3.5.5.2 Barostat studies

Michelsen et al[118] showed no change in rectal compliance after six months of chronic stimulation in 29 patients with faecal incontinence. Uludag et al[120] studied rectal compliance using isobaric phasic distension barsotat protocol in 15 patients undergoing temporary SNS reporting no change in rectal compliance with stimulation. However, as reported above, the authors reported changes in the sensory rectal function demonstrated by significantly reduced volume thresholds to distension and maximum tolerated pressure. This was also associated with significant reduction of calculated rectal wall tension for all filling sensations.

Roman et al[108] used a similar Barostat protocol to assess rectal functions after 3 months of chronic stimulation in 18 patients implanted for FI. They demonstrated no significant change in rectal compliance.

The significant inconsistency of findings in relation to rectal compliance (between barostat and non-barostat studies) is possibly a representation of the different methods used in different studies. However another factor is potentially the timing of evaluation of rectal compliance.

3.5.6 Rectal contractility (ambulatory rectal manometry)

Rectal contractility has been rarely studied in the context of SNS. Measurement entails ambulatory rectal manometry which is technically difficult and demanding. Vaizey et al [77] studied rectal contractility in 9 patients undergoing SNS and reported an apparent decrease in the number of rectal motor complexes as well as specific qualitative changes with stimulation. Altomare et al [98] studied two patients with 24-hour rectal manometry and similarly reported reduction of the spontaneous rectal motility complexes after meals and on awakening.

3.5.7 Rectal mucosal doppler flowmetry

Rectal mucosal blood flow measurement using laser Doppler flowmetry has been shown to be reproducible, quantitative, indirect measure of extrinsic autonomic nerve activity[121].Kenefick et al studied the nature of effect of chronic SNS in 16 patients with permanent SNS implants for faecal incontinence on Rectal Doppler Mucosal Blood Flow (RDMBF) using this technique[122]. They demonstrated a marked effect on the rectal mucosal blood flow with a statistically significant increase in the median flux with stimulation in a rapidly reversible and dose-dependent (up to level of stimulation of 1.0 V) manner, suggesting that SNS influences the autonomic innervations of the anorectum.

3.5.8 Pan-colonic motility and transit

Stimulation of the sacral nerves might be believed to be associated with motility effects on the distal colon only as the proximal extent of innervation by the S3 and S2 nerves is the distal transverse colon[123], however some studies have demonstrated otherwise. The establishment of long recto-colonic afferent pathways which are capable of inducing proximal colonic propagating pressure waves in response to rectal chemical stimulation[124] might clarify the potential underlying pathways of such an effect.

In a study of 8 female patients with long term constipation of mixed nature (reduced frequency and difficulty in evacuation symptoms but with scintigraphic evidence of slow transit), Dinning et al[125] examined colonic motor patterns using a colonoscopically-placed pan-colonic manometry catheter both with and without S2 and S3 stimulation in a double-blinded fashion. They demonstrated that SNS significantly increased frequency of both antegrade (stimulation of S3) and retrograde (stimulation of S2) Propagating Sequences (PS). This was also associated with increased frequency of the High Amplitude Propagating Sequences (HAPS) and the frequency of PSs which propagate more than 30 cm along the bowel. Six out of the eight patients completing the subchronic stimulation stage reporting a favourable clinical result demonstrated by increased frequency of defecation and reduced laxative use. The significance of the observed increase in retrograde motility with S2 stimulation is unclear, especially since one patient in the study who continued with S2 stimulation for the screening phase following the acute testing phase reported a positive response and increased frequency

of defecation. S2 stimulation similarly to S3 stimulation was associated with the induction of HAPS and prolonged PSs which are patterns associated with luminal transport and defaecation.

Uludag et al[126] assessed the potential effects of chronic SNS on bowel motility by examining bowel frequency and Colonic Transit times (using a marker study) in 13 patients who underwent permanent implantation for faecal incontinence. Interestingly, they demonstrated that these patients had significantly reduced frequency of bowel motions with the stimulation. Transit study performed before and one month after chronic stimulation showed no significant change in segmental or total colonic transit times.

Michelsen 2008[127]studied 20 incontinent patients who have been treated successfully with SNS using scintigraphy to assess colorectal transport during defaecation. They demonstrated reduction in the antegrade transport from the ascending colon and an increase in the retrograde transport from the descending colon at defaecation with no accompanying change in the defaecation scores.

3.5.9 Effects on Central Nervous System (CNS)

Studies have demonstrated that SNS influences not only the local somatic and autonomic nerves but also the central nervous system.

Braun et al[128] conducted electroencephalogram (EEG) studies on 10 patients with successful S3 permanent implants (for bladder dysfunction) whilst cyclically turning the device ON and OFF revealing that stimulation was associated with a specific evoked sensory cortical potential in all patients regardless of whether they were aware of the stimulation or not. The authors suggested that neuromodulation is probably mediated through supra-spinal areas. The exact site of generation of this evoked potential is still speculative. Interestingly Wyndaele[129] suggested that this supra-spinal influence may play a role in influencing the clinical response, as in a separate study it was demonstrated that the sensory mucosal bladder changes secondary to stimulation were equally present in both responders and non-responders[129] suggesting that success depends on more than just influencing the local reflexes.

Sheldon et al[130] conducted serial cortical mapping with transcranial magnetic stimulation before and immediately after temporary SNS in ten women with faecal incontinence, revealing changes of cortico-anal representation and overall excitability.

In a further study by the same group, changes to the excitability of the cortico-anal pathways were also demonstrated [131]. Healthy volunteers were subjected to 3 protocols of rapid-rate lumbosacral magnetic stimulation (Sham, 5Hz and 15Hz) whilst the effect on the anal sphincter as well other body muscles was studied with Electromyogram (EMG).

The conclusions of the last two studies were different as one showed reduction in corticoanal excitability whilst the second showed an increase. However, the two methodologies were significantly different and the patient selection was also different leading to two different patient groups.

3.5.10 Cellular and histological changes

Enteric neuroscience has significantly expanded our understanding of the neurochemistry and physiology of the visceral sensorimotor function. Several neuropeptides and membrane-bound receptors are found to be important to normal function and are dys-regulated in functional and inflammatory disease. These include epitopes such as Substance P, Vasoactive Intestinal Peptide (VIP) and Calcitonin Gene-Related Peptide (CGRP) [132, 133].

In a study to assess the change in peripheral expression of these various neural epitopes in response to SNS, Gooneratne et al[134] studied 8 rectal mucosal biopsies at three different time points (pre- stimulation, post- temporary SNS and 90 days after permanent implantation) in 12 patients who underwent temporary SNS (10 proceeding to permanent implantation) as well as in control subjects. They demonstrated a significant decrease in the percentage area of immunostaining of Substance P with SNS (compared to baseline) in patients who developed a positive clinical response to stimulation.

The study is limited by the fact that biopsies were mucosal and not full-thickness where a possible change in the neuronal plexus or dorsal root ganglia might be evident. However, it raises the questions of how SNS reduces the levels of substance P and whether this reduction is mechanistic or an epiphenomenon of stimulation or clinical response. Nevertheless, this study clearly opens a new ground of understanding potential changes and effects of SNS at the peripheral level and further work is definitely required to further explore this area.

3.5.11 Animal studies

3.5.11.1 Motility studies

Hirabayashi et al[135] examined the colorectal motility patterns during spontaneous defecation and following sacral nerve stimulation in a dog model using force strain gauge transducers operatively implanted in the proximal, distal and sigmoid colon, rectum and internal anal sphincter. Twenty six incidences of spontaneous defecation in four Mongrel dogs were recorded, revealing a pattern of giant migrating contractions of the colon propagating to the rectum with associated relaxation of the rectum before their propagation and relaxation of the internal anal sphincter during their propagation. The first, second and third sacral nerves were stimulated individually in six dogs, producing a motility pattern resembling those of the colon, rectum and internal anal sphincter during spontaneous defaecation (contractile movements were propagated from the distal colon to the rectum with associated relaxation response in the rectum and IAS),

suggesting the possibility that the coordinated movement of defaecation is activated through the sacral nerves.

3.5.11.2 On selective stimulation

In an experimental animal study involving 5 dogs, Bhadra et al[136] demonstrated that selective stimulation of the small diameter parasympathetic fibres in the sacral anterior roots without activating the larger somatic fibres to the EAS was possible using Quasitrapezoidal (Qzt) electric pulse waves. He demonstrated that the average evoked sphincter pressure with Qzt stimulation was significantly lower than with Rectangular (Rct) pulse stimulation with no significant difference in the evoked rectal pressures in the two cases. Furthermore, the authors demonstrated in 3 dogs that the mean mass of expelled bowel contents with Qzt stimulation was significantly higher than that with Rct stimulation, suggesting that bowel evacuation could be optimized by selective evacuation of the parasympathetic sacral roots which selectively suppress evoked EAS response without suppressing the evoked rectal contractions.

3.6 Do different stimulation parameters influence reported physiological changes?

It is unknown whether the various physiological responses to SNS are dependent on changes of Pulse Frequency or the other stimulation parameters. In clinical practice, stimulation parameters in-use have been fixed over time, based on the original settings

used historically to treat patients with bladder dysfunction (pulse frequency of 14 Hz and pulse width of 210 micro-second).

However, other studies have shown that the response of the IAS varied according to the stimulus frequency[137, 138]. Others have shown that alteration of rectal compliance following afferent nerve (dorsal genital nerve) stimulation in spinal injury patients appeared to be augmented with increased frequency of the stimulating current[139].

Dinning et al[125] showed that rectal motor response wasn't altered by changing Pulse Frequency to 300 or 400 micro-second.

However, Dudding et al[140] showed in a study of 12 patients that with alteration of stimulation parameters (lowering pulse width to 90 micro-second or increasing frequency to 14 Hz) around 67% of patients experienced a subjective improvement in clinical symptoms. The study also suggested that acute alterations of settings were associated with changes in rectal compliance; however details of order of changes and any potential order effect were not detailed or taken into account.

3.7 Predictors of clinical outcomes

Most patients can be biased to report or exaggerate the degree of a positive clinical outcome following PNE in pursuit of that magic answer to their significantly distressing and life-impairing set of symptoms. This might be part of the explanation of the

occasional lack of reproducibility of clinical outcome when patients proceed to having the permanent implant. A test predicting clinical outcomes of PNE and aiding patient selection for this procedure will be potentially a very helpful tool.

Although some authors believe that a successful clinical outcome with PNE is always reproducible with stimulation with a permanent implant[141], others report different experience[92, 107]. Also, in urological practice it was reported that as much as 25% of those who undergo permanent SNS for bladder dysfunction fail to exhibit the favourable clinical response they reported with the temporary stimulation[142, 143].

In an attempt to assess whether anorectal electrophysiological testing have any predictive value to the clinical outcome of PNE, Altomare et al[144] retrospectively studied the correlation between results of sphincter EMG, Pudendal Nerve Motor Latency (PNML) and Evoked Sacral Potentials (ESP) and the clinical outcomes in more than 60 patients who underwent PNE for faecal incontinence secondary to mixed aetiology including some neurological causes. They reported that normal sphincter EMG was significantly related to positive clinical response to PNE with a positive predictive value of 81%, Sensitivity of 44% and specificity of 81%. PNML on the right side did not correlate significantly with outcome, whereas a weak statistical significance was detected for a normal PNML on the left side; however both had a low positive predictive value and sensitivity. Data on ESP did not correlate with clinical outcomes and were too few to achieve statistical reliability. The authors, whilst stating that their data show that the functional level of the EAS expressed by EMG can predict the outcome of PNE with

an acceptable positive predictive value and sensitivity, highlight rightly that the neurophysiologic basis underlying this positive correlation is difficult to interpret as the effects of SNS on the EAS are not well understood.

Dudding et al[145] examined a cohort of 81 patients who underwent temporary SNS over a 10-year period to identify factors predictive of outcome. A low threshold to obtain a motor response during lead insertion was associated with improved outcome and the presence of evidence of anal sphincter trauma was associated with a greater risk of failure.

Roman et al[108] in a study of rectal functions in 18 patients with permanent implants for FI demonstrated that the only significant difference noticed between responders and non-responders (at 3 months) in his cohort was a significantly lower baseline MTV in the responders' group, suggesting that increased rectal capacity may represent a predictive factor of failure of SNS for FI.

It is to be mentioned here that all those studies are retrospective studies and therefore they can not conclusively answer the question. Prospective validated cohort of large registry data is required.

Chapter 4

Project Aims

4.1 Project theme

The theme of this project is to explore the underlying mechanisms of Sacral Nerve Stimulation in faecal incontinence. I designed a number of studies to examine various aspects of anorectal physiology in patients undergoing temporary SNS for intractable faecal incontinence. The focus of all studies was on the potential mechanisms of action and although relevant clinical data were presented, these are essentially mechanistic studies and no attempt at drawing major conclusions from the clinical findings was made.

The project included four component studies:

a) the examination of rectal compliance and rectal physiological properties with SNS

b) the examination of the effect of device ON/OFF alteration on anal pressures

c) the examination of RAIR variables with SNS

d) the examination of rectal evacuation and structural pelvic floor changes with SNS utilising MR proctography

The main concept behind these experiments is to establish whether the physiological effects of SNS in faecal incontinence are due to a direct efferent effect or as a result of indirect neuromodulatory function. Driven by this question, I designed the studies mentioned above to examine effects of SNS on autonomic- and intrinsic- mediated anorectal functions.

In this chapter, a summary of the aims and outcome measures of each study is presented. In the following chapters, the details of each study are presented; each in a separate chapter. Each chapter includes the introduction to the study with the details of the hypothesis behind the experiment followed by the methodology, results and a discussion of the study and its findings. In the final chapter I present a summary of the whole body of work and the conclusions drawn from it.

4.2 Aims, objectives and hypotheses of the research studies

The project included the following inter-linked studies:

Study	Description
Study 1	Changes in Anal pressures, Rectal Compliance, Rectal Sensory Thresholds and Rectal Mucosal Blood Flow with SNS
Study 2	Blinded examination of the effects of acute alteration of the status of stimulation on anal manometry during the course of temporary SNS
Study 3	Changes in RAIR with SNS
Study 4	Pilot study examining the possible functional Pelvic MRI changes associated with Temporary SNS.

4.2.1 Study 1

4.2.1.1 Title

Study of the changes in anal pressures and rectal physiological properties associated with temporary Sacral Nerve Stimulation

4.2.1.2 The research question

Does rectal compliance and rectal sensory thresholds change following temporary SNS in patients with faecal incontinence?

4.2.1.3 Study objectives (the measurable endpoints)

Primary Outcome	Secondary Outcomes
Change in rectal compliance and rectal sensory thresholds: Difference between baseline and post-temporary stimulation	1- Clinical symptomatology: a- Wexner incontinence scores b- Bowel diaries 2- Other anorectal physiological parameters: a- Anal resting pressure b- Anal squeeze pressure c- Electrical Anal and Rectal sensory thresholds d- Rectal Doppler Mucosal Blood Flow (RDMBF)

4.2.1.4 The underlying hypothesis

I hypothesized that SNS results in a consistent and persistent pattern of change in rectal compliance (an autonomic-facilitated function) with increased rectal compliance in incontinent patients treated with SNS.

4.2.2 Study 2

4.2.2.1 Title

Blinded examination of the effects of acute alteration of the status of stimulation on anal manometry during the course of temporary SNS

4.2.2.2 The research question

What are the physiological effects of acute alteration of SNS status on anal manometry ?

4.2.2.3 Study objectives (the measurable endpoints)

The measureable endpoints in this study were anal pressures (resting and squeeze) during the two alternating device settings (ON and OFF).

4.2.2.4 The underlying hypothesis

I hypothesized that acute alteration of SNS settings will not be associated with acute change in anal pressures as the process of SNS is a complex process of neuromodulation rather than a direct efferent stimulation of target muscle.

4.2.3 Study 3

4.2.3.1 Title

Changes in RAIR parameters with SNS.

4.2.3.2 The research question

Are there changes in any of the parameters of the RAIR in patients with faecal incontinence following temporary SNS?

4.2.3.3 Study objectives

The measurable endpoints in this study were as follows:

Primary Outcome	Secondary Outcomes
RAIR parameters (baseline and post-SNS)	1- Clinical symptomatology: a- Wexner incontinence scores b- Bowel diaries 2- Other anorectal physiological parameters: a- Anal resting pressure b- Anal squeeze pressure c- Rectal Sensory thresholds 3- RAIR parameters with acute alteration of device status at the end of temporary stimulation phase

4.2.3.4 The underlying hypothesis

I hypothesized that RAIR variables will change with SNS as the neuromodulation associated with SNS is believed to influence the intrinsic anorectal nerve pathways.

4.2.4 Study 4

4.2.4.1 Title

Pilot study examining functional pelvic MRI changes associated with Temporary SNS

4.2.4.2 The research question

This is a pilot study to explore the impact of SNS on pelvic floor function: Are there any changes in pelvic floor function following temporary SNS in patients with faecal incontinence?.

4.2.4.3 Study objectives

This is a pilot observational study examining the following outcomes:

a) Anorectal angle at rest and change on strain

b) Rate and quality of rectal emptying

c) Level of pelvic floor descent via a reference line

4.2.4.4 The underlying hypothesis

This was an exploratory pilot study designed to look at the function of the pelvic floor following temporary SNS utilizing MR proctography in a novel approach.

4.3 Overview of Design

The project design evolved over the study time period with inclusion of all patients undergoing SNS for faecal incontinence at the department.

4.3.1 Study 1

This was a prospective single-group cohort observational study in which a series of measurements are taken at two different chronological time points to assess the physiological changes associated with SNS.

The clinical and physiological assessments will be undertaken at baseline (before SNS) and at the end of temporary SNS phase (usually 2-3 weeks after insertion of temporary SNS wire).

Inclusion and Exclusion criteria:

All patients who are undergoing SNS for faecal incontinence were eligible for enrolment in the study. No exclusion criteria.

4.3.2 Study 2

Patients who were recruited to Study 1 were also approached for this study (See *Figure 4.1* showing study flowchart). The aim is to repeat the anal manometry measurements twice in a blinded fashion with the SNS device ON and OFF.

The device settings were blinded to the patient and the investigator; a person who is not involved with performing or analyzing the measurements undertook the changing of the device settings. Additionally, Closed Envelope randomization was used to decide the order of the ON/OFF arrangement.

Inclusion and Exclusion criteria:

All patients who were recruited to Study 1 were approached to participate in this study.

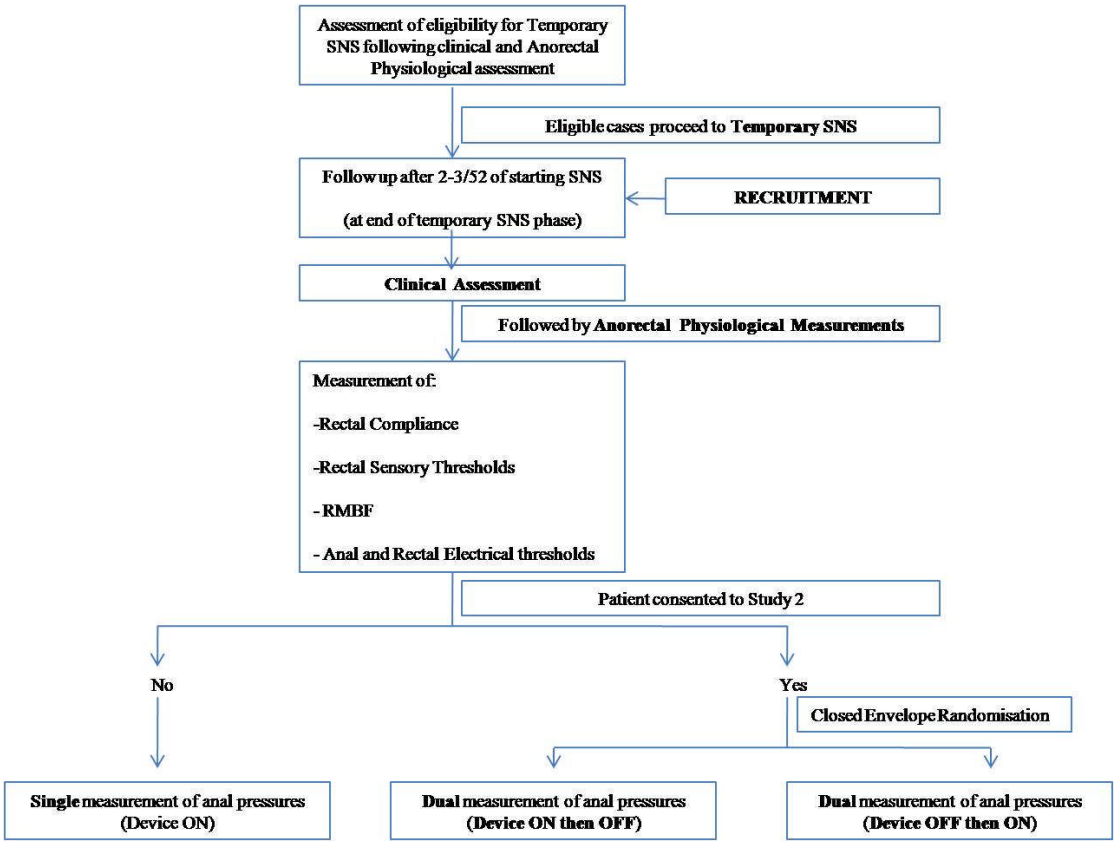

Figure 4.1 – Flowchart showing the recruitment process for Study 1 and Study 2

4.3.3 Study 3

This was a prospective single-group cohort observational study in which RAIR measurements were taken before and after temporary SNS.

Inclusion and Exclusion criteria:

All patients who are undergoing SNS for faecal incontinence were eligible for enrolment in the study. No exclusion criteria.

4.3.4 Study 4

This was a single-group prospective study. Patients who were undergoing temporary SNS were approached. Functional pelvic MR proctography was performed before and at the end of temporary SNS phase.

The MR proctography was performed by specialist radiographer and the analysis of images was performed by a specialist GI radiologist whilst blinded to the patients demographics and clinical data.

Inclusion and Exclusion criteria:

All patients who are undergoing SNS for faecal incontinence were eligible. Patients who had contraindications for undergoing MRI studies (e.g. indwelling cardiac pacemakers) were excluded.

Chapter 5

Methods

5.1 Chapter layout

In this chapter, I will describe in detail all the clinical and experimental methods utilised during the various studies of this project. Reference to this chapter will be made whenever those methods are referred to in the rest of the thesis.

5.2 Clinical assessment

A complete medical history including patient demographics, the onset and progress of anorectal symptoms, the nature of previous treatments, obstetric history (when relevant) and past medical and surgical history was obtained during the clinical assessment at baseline review. Clinical assessment also included examination of the anorectum. Additionally, patients were also asked to complete the following questionnaires:

a) Weekly bowel diary: a diary to record the number of bowel motions, episodes of incontinence or difficulty in evacuation together with information on stool consistency *(Figure 5.1)*. Patients were instructed to complete the diary for the period of 2-3 weeks at each assessment point.

b) Wexner incontinence scores: these validated questionnaires [33, 146] were used to assess the severity of incontinence at each assessment point *(Figure 5.2)*.

c) Quality of Life (QoL) questionnaires: the validated Short Form 36 QoL questionnaire was used to assess quality of life changes.

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Extension 73209

WEEKLY BOWEL DIARY

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Did you have a bowel action today? (Yes / No)							
How many bowel actions did you have today?							
What was the typical consistency of the stool? (0=hard, 1=formed/normal, 2=mushy, 3=watery)							
Did you have to strain to open your bowel? (Yes / No)							
Did you take any medications to help open your bowels? (Yes / No) – if Yes, what was it?							
Did you experience abdominal pain? (Yes / No)							
Did you experience abdominal bloating? (Yes / No)							
Did you have any difficulties with bowel control? (Yes / No)							

Figure 5.1 – The weekly bowel diary

Name:
Hospital No:

Wexner Faecal Incontinence Scoring System

Please note that all questions below refer to your **bowels** and not to your bladder.

Tableau I. – *Anal incontinence scoring system according to Jorge and Wexner [4].*
Score d'incontinence anale [4].

Type of incontinence	Frequency				
	Never	Less than once per month	Greater than once per month, Less than once per week	Greater than once per week, Less than once per day	Greater than or equal to once per day
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Requires pad	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4

0 = normal continence
20 = total incontinence

Thank you

To be completed by Unit

Total Score:

Figure 5.2 – Wexner Incontinence Scoring Questionnaire

5.3 SNS Technique

The temporary stimulation wire was inserted into S3 or S4 sacral foramen with the use of the Medtronic Insertion Kit 3065U (Medtronic, Minneapolis, MN) under fluoroscopy guidance in the operating theatre.

During the initial experience during the study time period, all procedures were performed under general anaesthetic (GA). However, as the experience of the operating surgeons were more developed, the option of undertaking the procedure under local anaesthesia (LA) was given to some patients. Therefore, later on during the study the procedure was performed under either general or local anaesthesia according to patient preference. Consequently, the choice of the wire placement site depended on the best motor (if under GA) or sensory response (if under LA) to acute stimulation. This represent a potential confounding factor in the study and is accepted as one of the study limitations.

The wire was secured in situ with dressings and was connected to an external stimulator (Medtronic 3650 Test Stimulator, Medtronic). Stimulation parameters were set with a pulse rate of 210 ms, pulse frequency of 14 Hz, and amplitude just at the sensory threshold. Stimulation was continuous for the longest possible duration between 2 and 3 weeks.

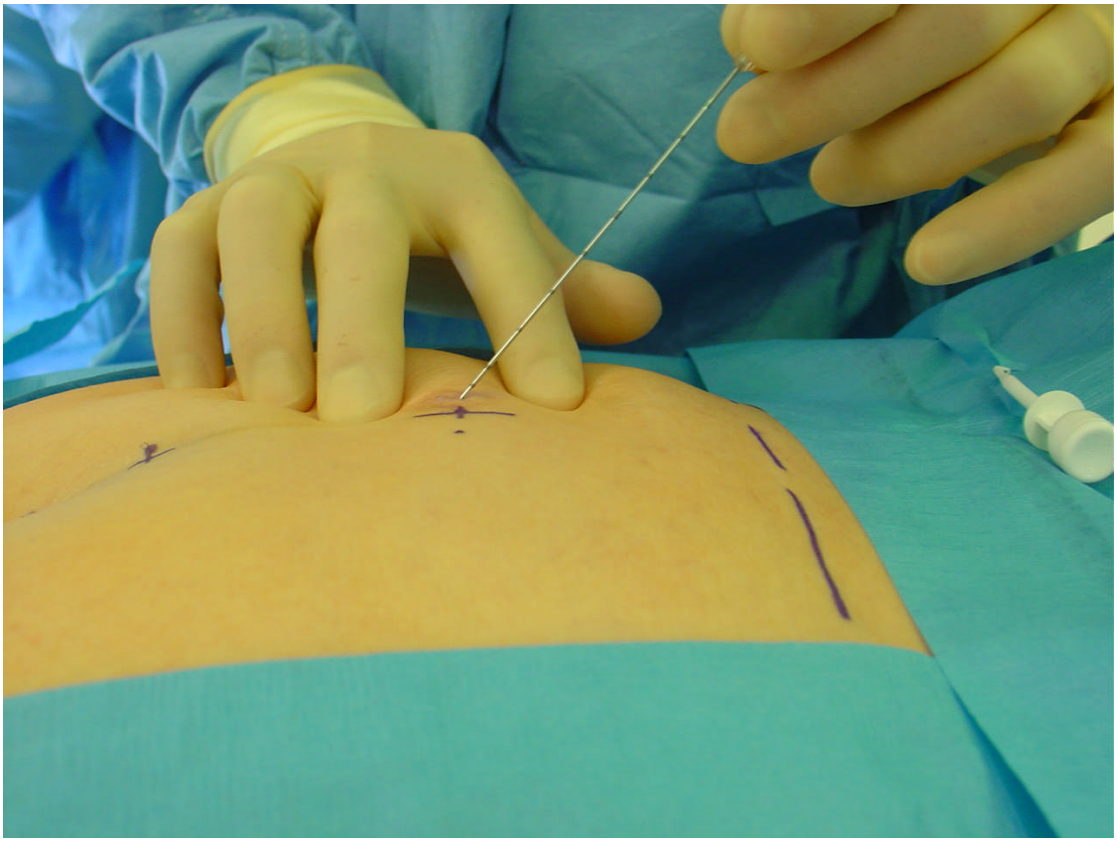


Figure 5.3 – Insertion of the temporary SNS wire. The canula used to localize the nerve prior to insertion of the stimulating wire.

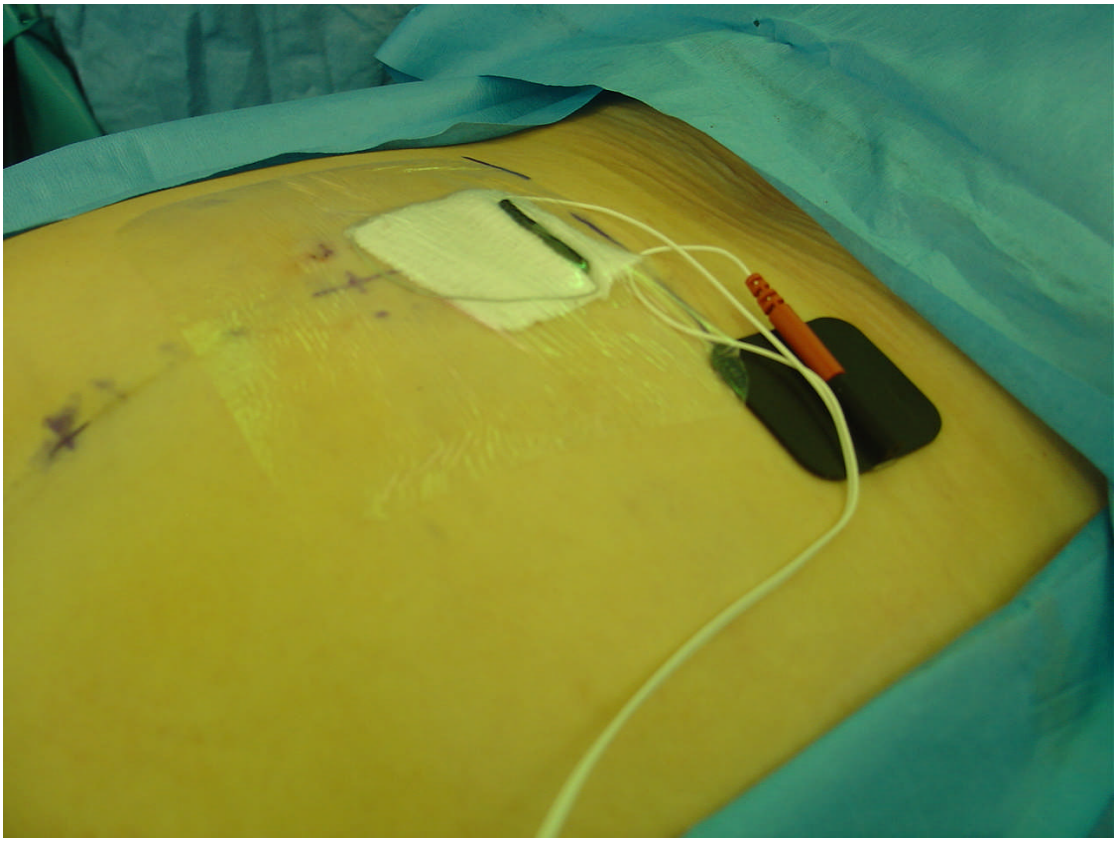


Figure 5.4 – The temporary SNS wire secured with dressings after insertion.

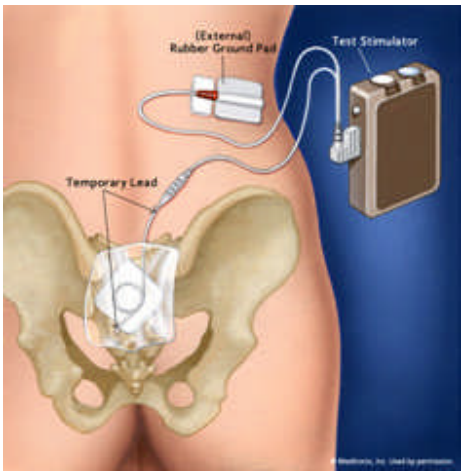


Figure 5.5 – Diagrammatic representation of the temporary SNS unit.

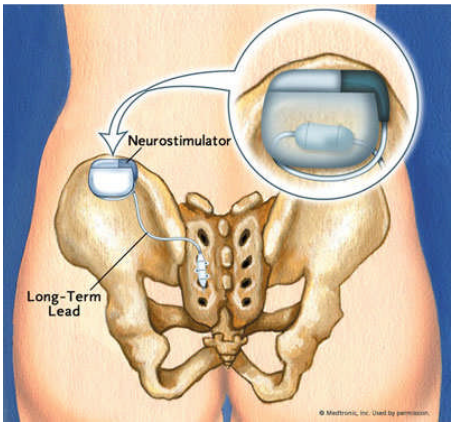


Figure 5.6– Diagrammatic representation of the Permanent SNS unit.

5.4 Anorectal physiological tests

5.4.1 Anal manometry

A water perfused manometry system (Ardmore Healthcare, Bucks, UK) with a pump (Mui Scientific, Ontario, Canada) was utilized *(Figure 5.7)*. The system was controlled by specialist computer software supplied by Medical Measurement Systems (MMS, Enschede, Netherlands).

A single use latex free 8-channel anorectal manometry catheter (Ardmore Healthcare, Bucks, UK) was used *(Figure 5.8)*. Sterile water was used for system perfusion and the standard perfusion rate of 0.6 ml/minute was used.

The manometry catheter had an external diameter of 3.9 mm with 8 recording openings 'holes' arranged radially 3cm from the tip. Each recording opening was separately perfused and recorded *(Figure 5.9)*. The system was linked to the attached computer using peripherals supplied by MMS (Enschende, Netherlands).

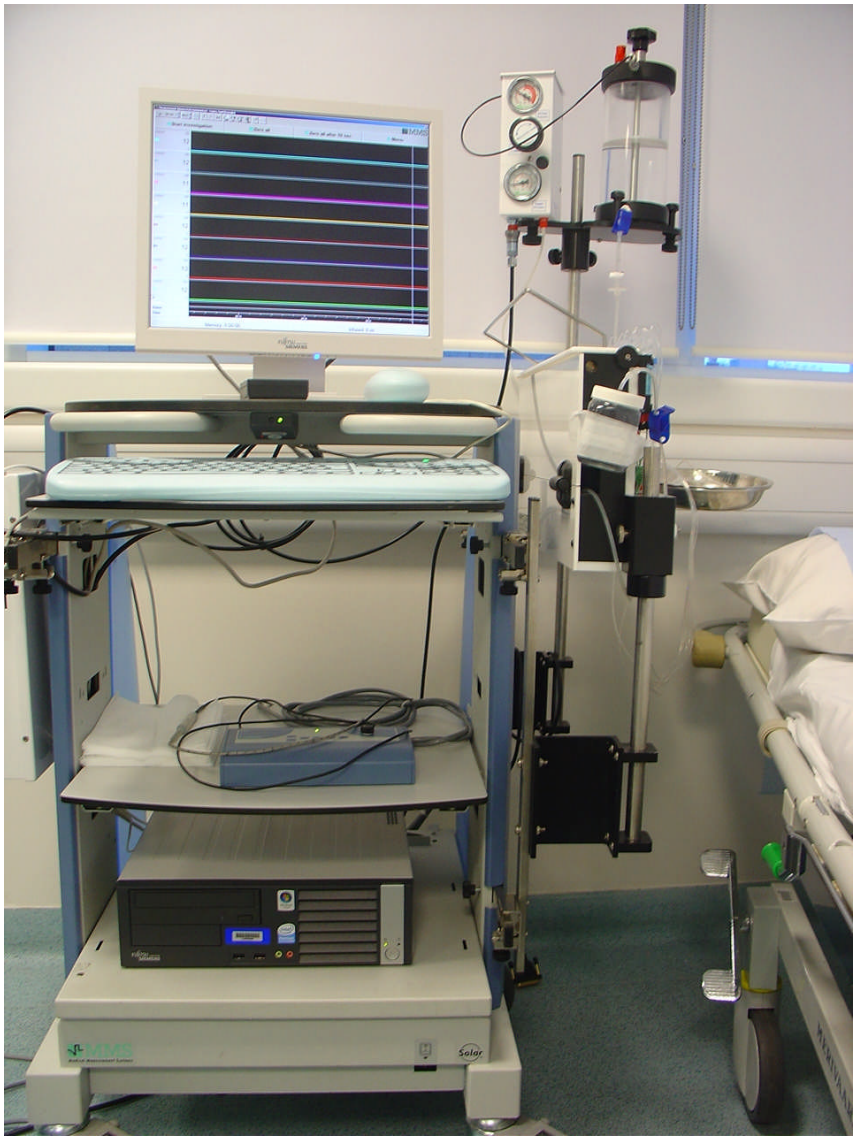


Figure 5.7 – The manometry stack

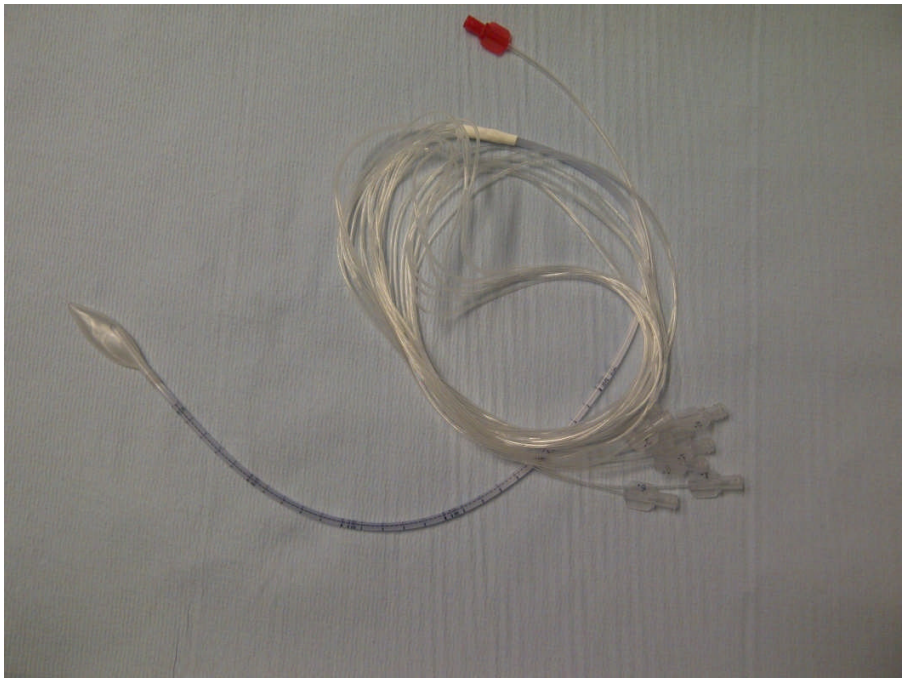


Figure 5.8 – Manometry catheter

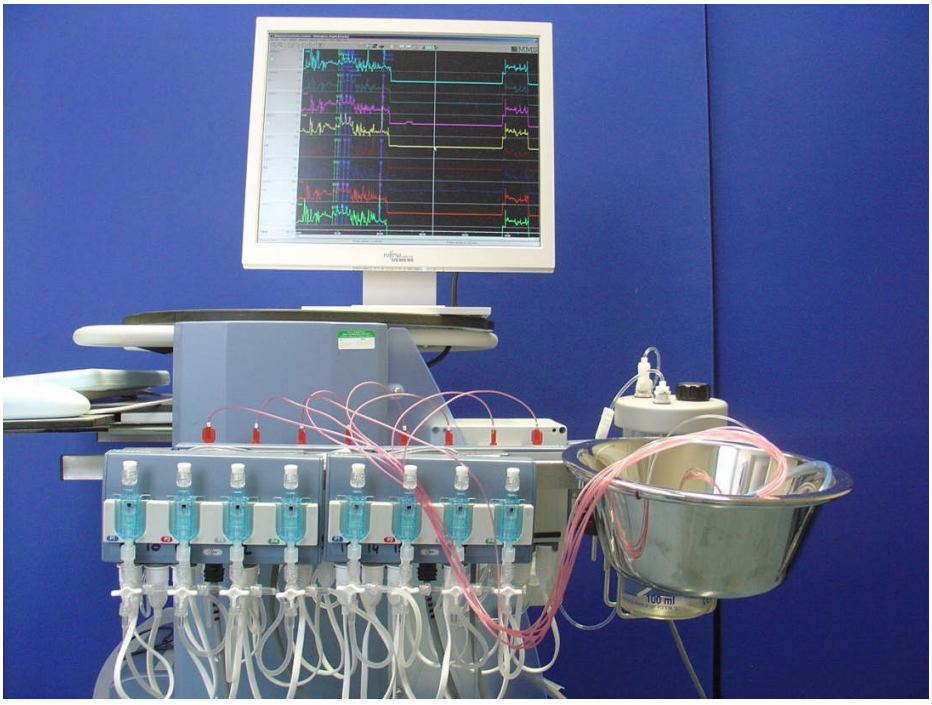


Figure 5.9 – Manometry sensors

The system was an orthostatic pressure measurement system and it was zeroed when the tip of the catheter was at the level of the anal canal. Any pressure changes were determined by occlusion of the openings at the catheter tip. The pressure change was recorded by external pressure transducers which converted the recorded pressure to an electronic signal. This signal was then processed by the MMS software and displayed on the visual display unit of the computer. The readings from each radial recording opening were processed separately to give an 8-channel recording. The recording was stored on the password-protected Gastroenterology Department network. The pressures were quoted in cmH2O.

The station pull-through technique was employed. The subject was positioned in the left lateral position and the manometry catheter was zeroed and was then placed into the anal canal until the tip was in the rectum. This was determined by a reduction in the recorded pressure. The catheter was then withdrawn in 1 cm steps until a rise in pressure was re-observed. The catheter was further withdrawn in 1 cm steps until the highest pressures were recorded. The catheter was then left at this position to measure the resting anal pressure. The subject was then asked to voluntarily contract the anal sphincter and this was recorded as the anal squeeze pressure. This was repeated three times and the highest value was recorded. The subject was then asked to cough and the pressure change was noted as an involuntary contraction of the sphincters. The subject was then asked to squeeze for a period of 5 seconds to see whether they were capable of maintaining an endurance squeeze. A typical tracing of anal manometry is shown in *Figure 5.10*.

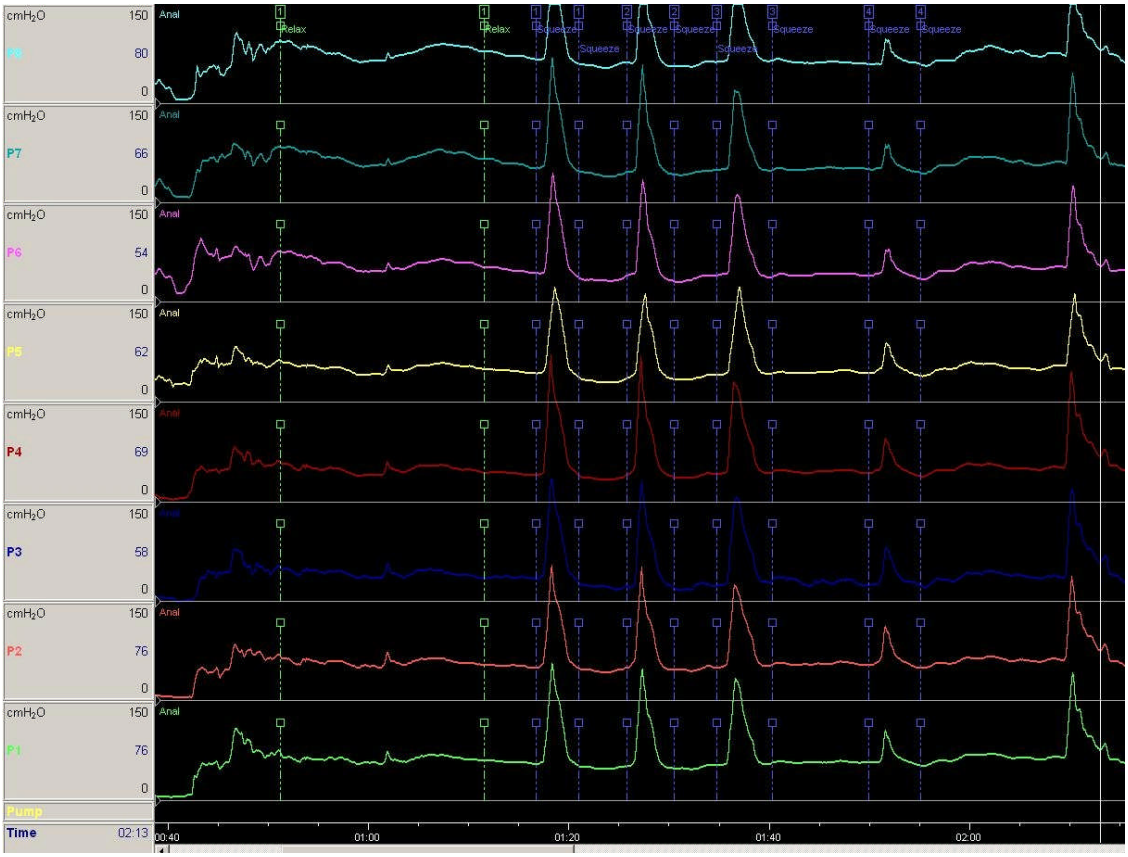


Figure 5.10 – Manometry trace

5.4.2 Rectal sensory thresholds to balloon distension

A latex balloon with a maximal capacity of 500ml was mounted on the anal manometry catheter (Ardmore Healthcare, Buck, UK) *(Figure 5.11)* and was used for assessing rectal sensation to distension. The balloon was controlled with a three-way tap at the end of the catheter. A 50 ml syringe (BD Medical, Drogheda, Ireland) was used for inflation.

With the subject in the left lateral position, the balloon was inserted through the anal canal into the rectum. The balloon was slowly inflated with air and the subject was

asked to report the following sensations: a) First Sensation (FS): when they first become aware of the balloon; b) Urge Sensation (U): when they feel the need to defecate; and c) Maximal Tolerated Volume (MTV): when they feel any discomfort or pain. The maximum inflation volume was 350 ml and no further inflation was performed when this volume had been reached regardless of what the subject had reported.

Figure 5.11 – Tip of the manometry catheter demonstrating the mounted balloon

5.4.3 Anorectal mucosal sensory thresholds to electric stimulation

A bipolar electrode (Gaeltech, Skye, Scotland) was used to assess mucosal sensory thresholds to electric stimulation. This was attached to an electrical stimulator (MMS, Enchende, Netherlands), which in turn was attached to the computer and was controlled

by the same MMS software. The use of bipolar electrode to test anorectal sensory thresholds is established since the experiment by Roe et al [147].

With the subject in the left lateral position, the bipolar electrode catheter was placed in the anal canal first and then the rectum to measure the anal and rectal sensory thresholds respectively.

In the anal canal, electrical stimulation was applied at 5 Hz with a pulse width of 0.1 msec; the current was incrementally increased (up to a maximum of 20 mA) until the subject reported the awareness of sensations which was described to the patient as similar to pricking sensation.

In the rectum, electrical stimulation was applied at 10 Hz with a pulse width of 0.5 msec and was incrementally increased (up to a maximum of 50 mA) until the subject reported the perception of any pain or unusual sensation.

5.4.4 Recto-Anal Inhibitory Reflex (RAIR)

The manometry catheter was pre-mounted with a balloon. With the subject in the left lateral position the manometry catheter was introduced into the anal canal and positioned such that a steady pressure trace was obtained with the balloon within the rectum. After giving the subject prior warning, the balloon was rapidly inflated with air to 50ml and was then rapidly deflated. Any pressure changes in the anal canal were

recorded. If it was not initially possible to elicit the reflex, the manometry catheter was repositioned and inflation/deflation repeated. A further attempt at eliciting the reflex by the inflation of 100ml was performed if the reflex was not elicited after catheter repositioning.

The measured parameters of the RAIR were as follows *(Figure 5.12)*; a) the excitation latency, b) amplitude of reduction, c) percentage of relaxation as compared to the resting anal pressure, d) the recovery time, and e) the total reflex duration. The point at which anal pressure returned to two thirds of its original value point was deemed to be the end of the reflex.

The excitation latency was measured as being the time taken from maximal stimulation to when that anal pressure returned to its resting level. The beginning of the recovery time was when the amplitude reached its nadir. The total duration of the reflex was measured from the maximal positive inflexion to the point at which the amplitude returned to two thirds' of the original resting pressure. The resting anal pressures used to determine the amplitude of relaxation were determined for each chosen trace as the value of resting anal pressure with the trace most stable just before the excitation phase.

The RAIR was accepted to be present if the amplitude reduction was at least 25% of the resting anal pressure. If the RAIR was observed in more than one of the circumferentially-placed 8 channels, the trace which measured the greatest amplitude reduction was chosen for further analysis.

A manometry tracing from a subject displaying the RAIR is shown in *Figure 5.13*. In this subject, the P5 channel had the greatest amplitude reduction and was therefore chosen for further analysis.

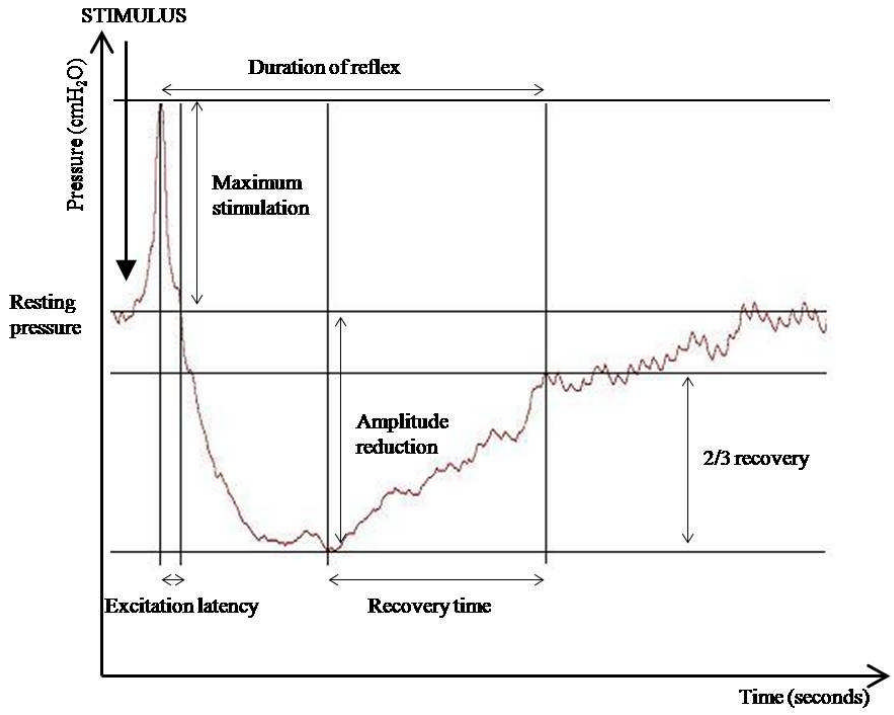


Figure 5.12 – The various components of RAIR wave on a manometry trace: a) Excitation peak: initial increase in the resting pressure associated with the sudden rectal distension. b) Latency (X-Y): duration from the point of excitation peak back to the baseline pressure. c) Point of maximum relaxation (Z): lowest point of resting pressure secondary to reflex IAS relaxation. d) Recovery time: (Z-Z1): the duration between maximum relaxation and the point at which the resting pressure recovers to two thirds its baseline. e) Total reflex duration (X-Z1): calculated as the duration from the point of the Excitation Peak to the point two thirds' the recovery (Z1).

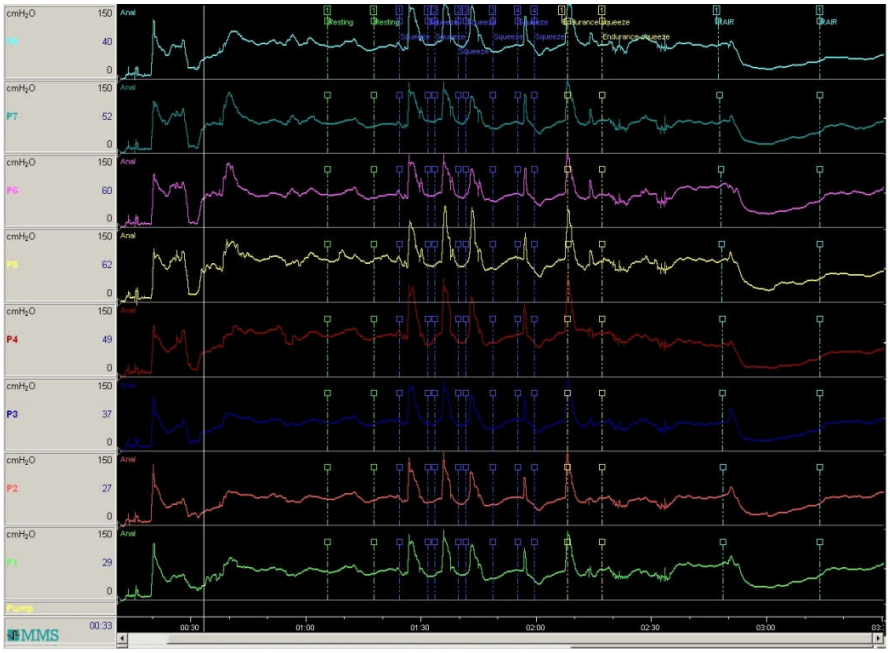


Figure 5.13 – Manometry trace showing the recorded RAIR

5.5 Rectal compliance and assessment of rectal sensory thresholds using barostat

A mechanical barostat (Distender II, G&J Electronics, Ontario, Canada) was used for pressure-volume measurements *(Figure 5.14)*. The mechanical instillation of air allowed for the standardization of flow rate and accurate measurements.

A specialized dual lumen silicon catheter, manufactured for use with the barostat (Mui Scientific Inc., Ontario, Canada) was used. The length of the catheter was 1.5 meter. One lumen was used to infiltrate air into the bag and the other lumen was used to

measure pressure within the bag. At the distal end of the catheter there were two ridges spaced 10cm apart designed to secure the bag over the catheter *(Figure 5.15)*.

Figure 5.14 – The barostat machine

Figure 5.15 – The barostat catheter

The barostat bag had to have specific properties so that whilst it is distended and in contact with the rectal wall, the pressure measured within the bag equates to the pressure exerted on the bag by the rectum. For this to occur, the bag itself had to be infinitely compliant exerting no force of its own.

This means that Polyethylene rather than Latex (which had the problem of requiring a large initial pressure to stretch but then stretches very easily) had to be used.

There are two ways of designing an infinitely compliant bag. Either a balloon which is infinitely compliant up to its maximum volume, or a fixed large-volume non compliant

bag which has a maximum volume greater than the maximum volume of the rectum. Krogh et al demonstrated that results using the 'oversized bag' are more reproducible[148].

For this study a 20 x 15 cm polyethylene, over-sized, non-compliant bag with a maximum volume of 600ml (CT-BP500R bag, Mui Scientific, Ontario, Canada) was used to measure compliance *(Figure 5.15)*.

5.5.1 Catheter placement

The catheter with the bag attached was lubricated with K-Y jelly (Johnson & Johnson, New Jersey, USA) and inserted into the rectum. It was held in place by taping it to the buttocks if required.

5.5.2 Distension sequences

The following distension sequences were conducted:

1) Determination of the Minimal Distending Pressure (MDP) and Basal Operating Pressure (BOP):

The bag was distended at 1 mmHg increments. The pressure was maintained for 15 seconds at each step. To establish whether the bag was distended to the point of touching the walls of the rectum or not, the subject was instructed to breathe deeply whilst the

operator checks for any pressure variations. If these were not seen by 10mmHg, the MDP was set at that level (10 mmHg). The BOP was set at MDP + 2mmHg.

2) Conditioning distension sequence:

An initial conditioning distension was performed prior to the test (index) distension, as studies have demonstrated that a difference in the pressure-volume relationship between the first and second distensions but not with subsequent distensions thereafter [149].

The BOP was used as the starting baseline for this distension sequence. Sequential 4mmHg stepwise distensions were attained up to 20 mmHg, with each step lasting for 15 seconds. Air insufflations rate was 30 ml/second.

3) Index distension sequence:

This was commenced after the completion of the conditioning distension. Similar sequential 4mmHg stepwise pressure increments were used up to the maximum of BOP + 40mmHg. Each step however, lasts for 1 minute. Air insufflation rate was the same.

5.5.3 Calculation of compliance

5.5.3.1 Analysis of the pressure-volume data

A special software (Protocol Plus) provided by the barostat manufacturer (G&J Electronics, Ontario, Canada) was used to analyze the raw data recorded during distension sequences *(Figure 5.16)*.

The software was utilized to average the volume of air within the bag over the last 10 seconds of the each distension step. This usually reflected the volume of the bag in a stable stage of the corresponding pressure increment phase *(Figure 5.16)*.

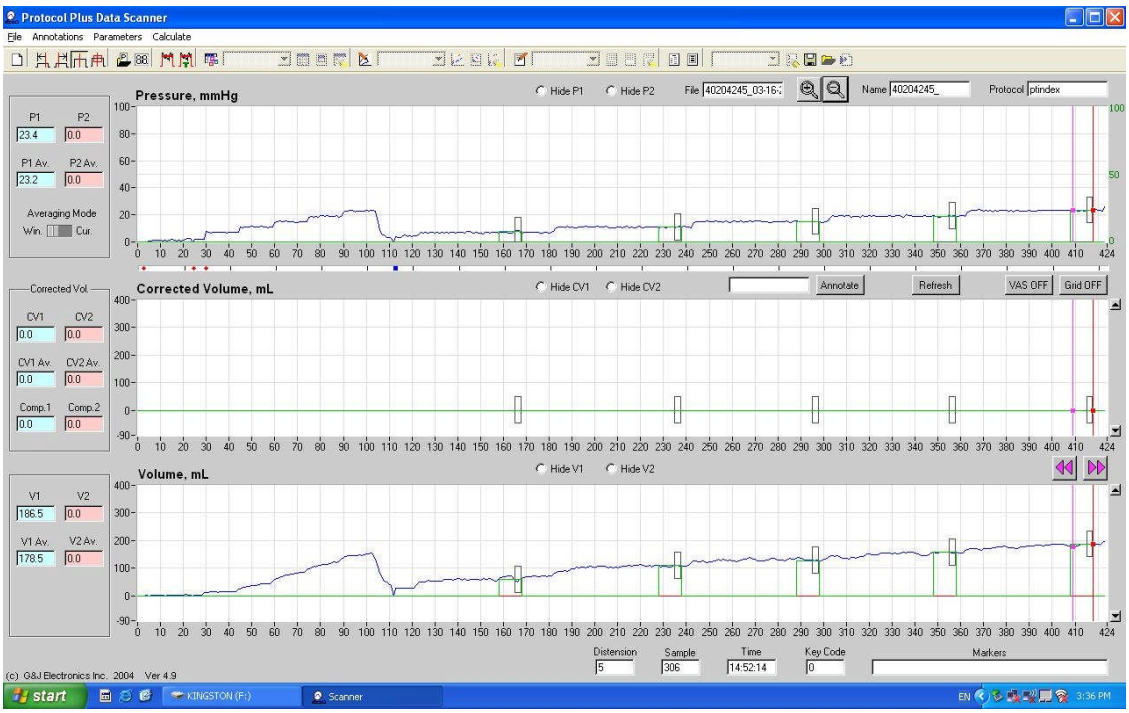


Figure 5.16 – The software used for analysis of volume-pressure data

5.5.3.2 Calculating compliance

The pressure-volume values were entered into Prism 4.0 (GraphPad Software Inc, CA, USA) to create a graphical representation of the values.

a) Sigmoidal relationship observed:

If a sigmoid relationship was observed, a best fit curve was computed and a tangent was then drawn to the steepest part of the curve. The gradient of this line was considered as the compliance of the rectum (measured in ml/mmHg) *(Figure 5.17).*

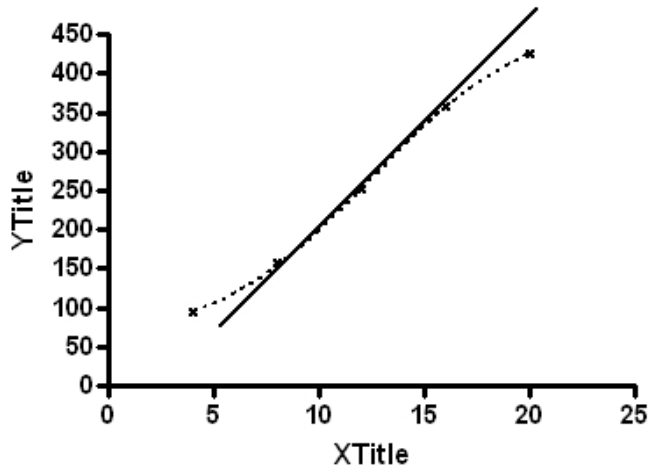


Figure 5.17 – Typical sigmoidal pressure-volume curve

b) Sigmoidal relationship not observed:

A linear relationship was identified between the pressure-volume values sometimes. In these occasions, a best fit line was computed and its gradient was taken to be the compliance value *(Figure 5.18)*.

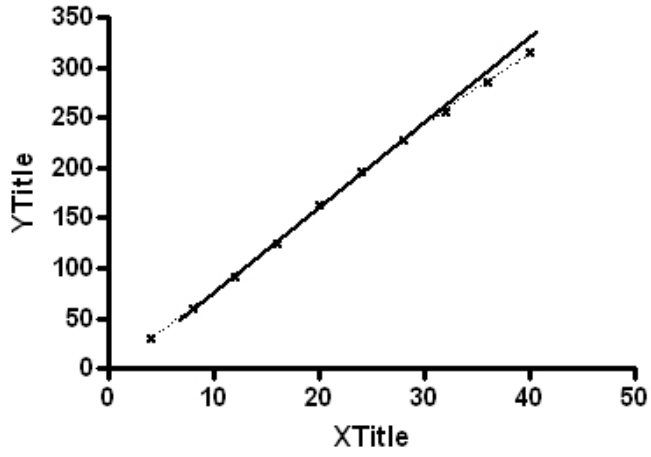


Figure 5.18 – Linear pressure-volume relationship curve

5.5.4 Rectal sensory thresholds assessment using barostat

Rectal thresholds to distension were assessed during the isobaric intrarectal bag distension. Patients were asked to report when they first perceived the following sensations during the index barostat distension protocol: first sensation, urgency to

defecate and maximal tolerated volumes. The volume and pressure at each threshold point were recorded.

5.6 Rectal Doppler Mucosal Blood Flow (RDMBF) measurement

A DRT4 laser Doppler flowmeter (Moor Instruments, Devon, UK) was used *(Figure 5.19)*. With the patient in the left lateral position, the probe was placed against the mucosa 10 cm above the lower limit of the anal margin. A recording was taken for 3 minutes after a stable reading was obtained. Normal reference range for the mean mucosal flux (155.4 – 210.2) was previously published by researchers in the same lab [121].

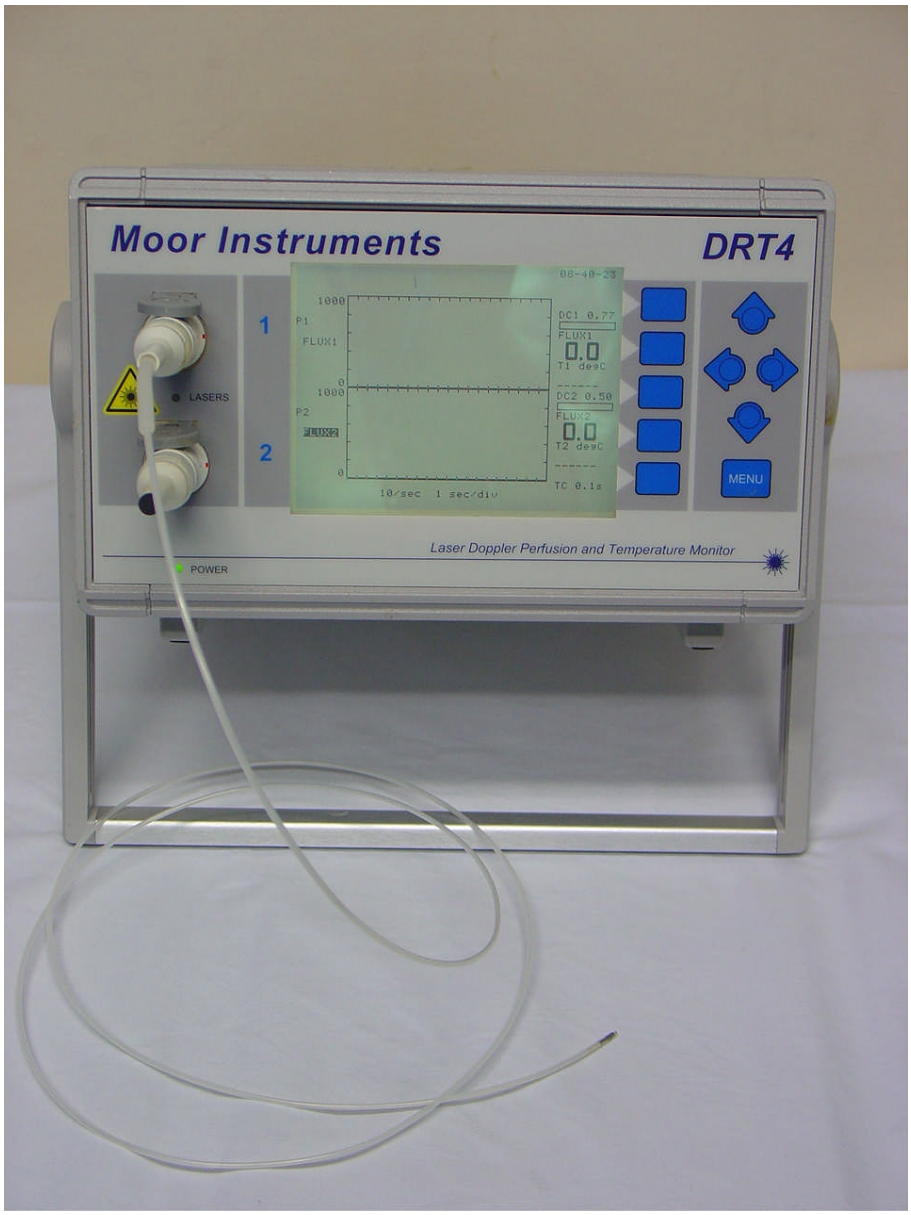


Figure 5.19 – RDMBF measurement device and Doppler probe

5.7 MR Proctography

MR proctography was performed in the standard approach in line with described techniques[150, 151]. A standard superconducting MR imaging system (1.5T Avanto, Siemens, Germany) was used. Examinations were performed with the patient in the supine position with slight flexion at the hips and knees. An absorbent pad was placed underneath the patient to contain the evacuated contrast.

The rectum was prepared with the administration of a phosphate enema (Fleet enema, Fleet Company, Virginia, USA), to ensure rectal emptying before the examination. Before imaging, the rectum was filled with 150ml of ultrasound contrast gel, which was instilled via three bladder syringes by an experienced practitioner. After the rectum was filled, the patient was placed supine on the imaging table as described above.

After localising images were acquired, dynamic True Fast Imaging with Steady State Precession (TrueFISP) sequence was performed in the midsagittal plane of the pelvis through the rectum at rest and during attempted evacuation of the rectal jelly. Imaging parameters were as follows: repetition time 4.25; TE-2.13 section thickness 5mm; 1 average. Images were repeated every 0.75 second for a total of 100 images. If the rectum had not cleared after the first attempt, sequences were run again during a further attempt at evacuation.

Patients were coached by the radiology technician performing the examination; a microphone and headset enabled communication. All images acquired were formatted into a cine loop presentation to enable assessment of the dynamics of both rectal emptying and pelvic floor movement

5.8 Data Analysis and Statistics

PASW® Statistics 18 software package (SPSS Inc, Chicago, USA) and StatsDirect statistical software package version 2.7.3 (StatsDirect, Cheshire, UK) were used to analyse the data.

The characteristics of the patients recruited were described with simple descriptive statistics: mean and s.d. or median and range for continuous variables according to the data's distribution, and percentages for categorical variables.

Most outcome measures were continuous variables, and analysis (pre- and post-SNS)was made using the paired t test or Wilcoxon's signed ranks according to the distribution of the data. P values of 0.05 or less were considered statistically significant.

Chapter 6

Patients

In this chapter, a description of the recruitment and ethics procedure is given, followed by the description of the demographics and basic clinical characteristics of the cohort of patients recruited to the study project.

6.1 Patient Recruitment

All potential recruits to the study were patients with feacal incontinence who were undergoing SNS.

These prospective participants were recruited from the following clinics:

i) Gastroenterology clinics at University College London Hospital (UCLH)

ii) Colorectal clinics at University College London Hospital

iii) Gastrointestinal Physiology department at UCLH

Patients were approached and invited to participate in the study. They were provided with a patient information sheet (PIS) to read in their own time. They then decided whether or not to participate and had until the time of their treatment (at least 4-6 weeks) to make their decision.

6.2 Ethics

The study was reviewed and approved by the Joint UCL/UCLH Committees on the Ethics of Human Research (reference 09/H0715/29).

6.3 Patients demographics

A total of 30 patients were recruited to the various studies in this research project. Twenty nine were females (96.6%). The median age of patients was 49 years (range 25-77).

6.4 Patients clinical characteristics

All patients had intractable faecal incontinence with ongoing symptoms for at least one year. All suffered at least weekly episodes of incontinence and their symptoms were significantly impacting their life style with mean Wexner scores of 14 ±3 [0=perfect continence, 20=worst possible incontinence].

Aetiology of faecal incontinence included obstetric causes (15 patients), idiopathic incontinence (7 patients), post-surgical (3 patients: 2 post STARR, 1 post pelvic surgery), scleroderma (2 patients), long standing rectal prolapse (1 patient), sphincter atrophy (1 patient) and sub-arachnoid haemorrhage (1 patient) *(Figure 6.1)*.

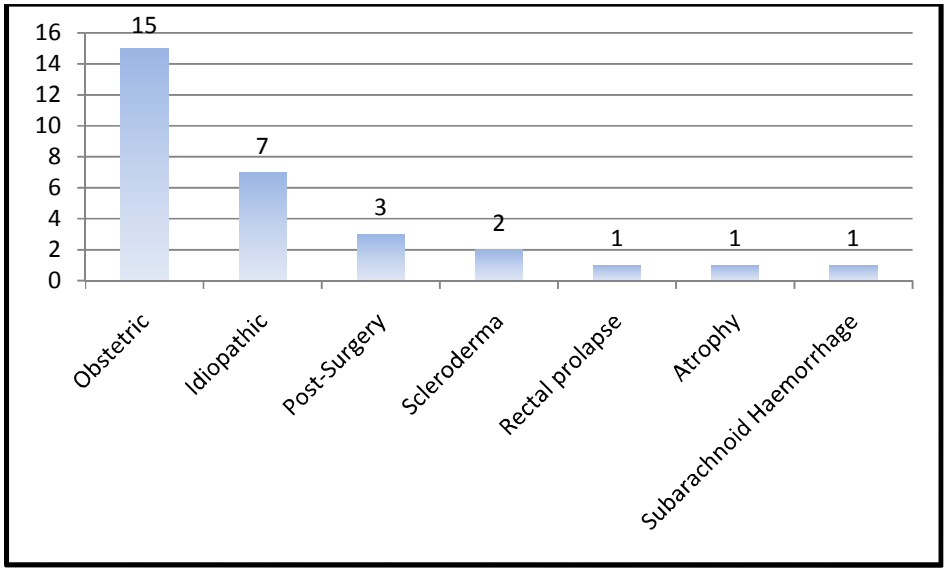


Figure 6.1 – Aetiology of faecal incontinence in the study cohort

All patients underwent Endo-Anal Ultra-Sound (EAUS) assessment at baseline. This showed intact sphincters in 17 patients (57%), atrophic sphincters in 5 (16.5%) and sphincter defects in 8 (26.5%) *(Figure 6.2)*. Sphincter repair had previously been performed in 11 patients of this cohort, seven of them having residual defects. Only one patient with a sphincter defect diagnosed at the time of presentation had not undergone repair prior to SNS.

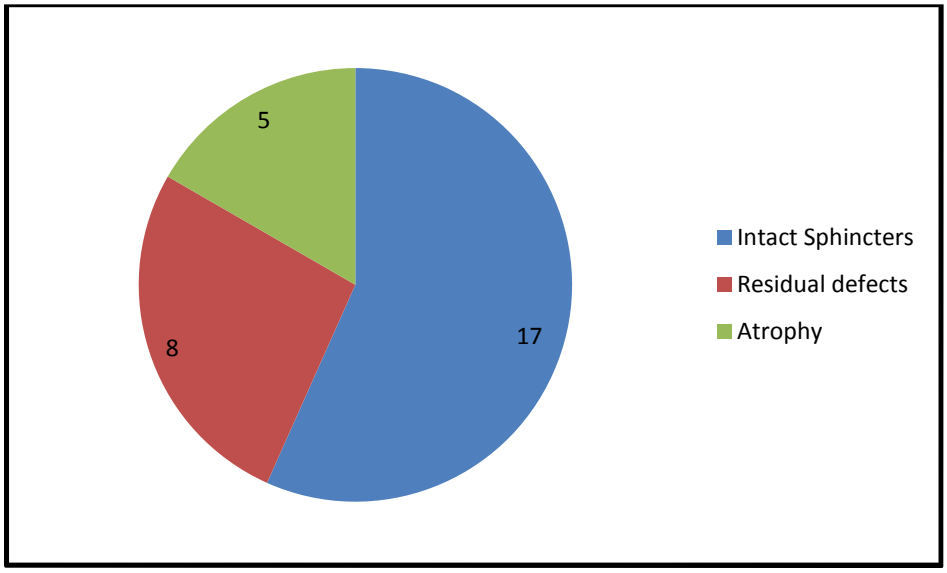


Figure 6.2 – Pie chart showing EAUS findings in the study cohort

6.5 Clinical Results

Twenty one patients (70%) had a significant clinical response to the stimulation, with Wexner scores significantly reducing from a mean of 14 (±3) to 7 (±4) (P<0.0001).

The median duration of stimulation in the whole cohort was 21 days (range 8-23); this did not differ between responders (21 days, 10-23) and non responders (21 days, 8-21) (P=0.0848, Mann Whitney) *(Table 6.1)*.

Clinical response was not influenced by the structural integrity of the sphincter as identified by EAUS (Fisher exact P=0.544).

Table 6.1 – Demographics and clinical data in Responders and Non-responders:

	Responders n=21	Non-responders n=9	P value
Sex	21 f	8 f, 1 m	0.3 ‡
Age	49 (37-72)	50 (25-77)	0.555 †
Aetiology of FI			0.059 ‡
Obstetric	12	3	
Idiopathic	2	5	
Post-Surgical	3	0	
Sphincter atrophy	1	0	
Scleroderma	2	0	
Subarachnoid haemorrhage	1	0	
Rectal prolapse	0	1	
Baseline Wexner scores	14 ±3	14 ±3	0.793 §
EAUS results			0.544 ‡
Intact	11	6	
Atrophy	3	2	
Defects	7	1	
Duration of stimulation	21 (10-23)	21 (8-21)	0.085 †
Follow up Wexner scores	7±4	14 ±4	**0.0006** §

† Mann Whitney U test
‡ Fisher exact test
§ un-paired *t* test

Chapter 7

Effects on anal manometry and rectal physiological properties

7.1 Chapter layout

In this chapter, I present the findings of the first study of the project which focused on examination of the changes in rectal physiological properties and anal manometry following SNS. The study examined the changes after temporary stimulation phase. An introduction to the study is presented, followed by description of the methodology, results and discussion.

7.2 Specific study rationale

As described in Chapter 3, SNS emerged as a therapeutic modality in the field of bladder dysfunction [71, 73, 75] and was later applied in the treatment of faecal incontinence in 1995 [76]. Since then it has gained wide recognition as a successful treatment in various functional pelvic floor disorders.

As previously mentioned, the majority of the studies which have examined rectal compliance in the context of SNS have used the rectal balloon infusion technique[77, 78, 91, 98], an inaccurate way of assessing the biomechanical properties of the rectum[148, 152].

I aimed in this study to examine the following two aspects: a) the change in anal pressures with SNS to further validate the finding most consistent in the literature that SNS is associated with an increase in anal pressures; b) rectal physiological properties;

namely: rectal compliance, rectal sensory thresholds and rectal Doppler mucosal blood flow.

I was driven by the hypothesis that SNS does not act merely through efferent stimulation of the nerve supply to the sphincter muscles; rather it acts through a more complex mechanism of neuromodulation where changes in one nerve pathway leads to changes in another through synaptic interactions. The complexity of clinical conditions to which SNS has a positive clinical outcome makes me favour this hypothesis. Additionally, previous experiments have demonstrated that the interval to sphincter contraction following the acute stimulation of S3 is much longer than would be expected if the contraction was a result of efferent stimulation [113].

I propose that SNS does influence the anorectal autonomic nerve function and therefore I hypothesised that rectal compliance (an autonomic-mediated anorectal function) will significantly change with SNS.

7.3 Patients and methods

7.3.1 Patients and clinical assessment

All patients undergoing temporary SNS were symptomatic for at least one year and had failed all conservative measures including dietary, pharmacological and biofeedback treatments. Routine pre-operative assessment included full clinical evaluation, anorectal

physiology studies and endo-anal ultrasound. Weekly bowel diaries detailing the frequency of bowel movement, the episodes of incontinence and stool consistency (for three weeks' period) and Wexner Incontinence Questionnaires were completed by the patient before and during the temporary stimulation phase. In agreement with most authors[76, 77, 79], a positive clinical response to stimulation was considered if there was at least 50% improvement in symptoms, however patients' subjective impression on the state of their symptoms was also taken in consideration.

7.3.2 Methods

SNS techniques, anal manometry, rectal compliance measurement, assessment of rectal sensory thresholds and rectal doppler mucosal blood flow measurement were all described in details in Chapter 5.

7.3.3 Statistical analysis

StatsDirect statistical software package version 2.7.3 (StatsDirect, Cheshire, UK) was used for data analysis. Data were mainly presented as median and range as it did not follow normal distribution. Baseline and post-stimulation results were compared using the Wilcoxon's Signed Rank test. A P value of less than 0.05 was considered statistically significant.

7.4 Results

Twenty three patients (22 female and 1 male) undergoing temporary SNS for intractable faecal incontinence over the period of 22 months were studied.

7.4.1 Patients and clinical results

The clinical characteristics and demographics of this study cohort (summarized in *Table 7.1*) were similar to the overall study cohort described in chapter 6.

Sixteen patients (70%) had a significant clinical response to stimulation, with weekly episodes of incontinence reducing from the mean of 5 (±2) to 1 (±2) ($P<0.0001$). Wexner scores were also significantly reduced from a mean of 14 (±3) to 6 (±4) ($P<0.0001$). Non-responders (7 patients, 30%) experienced some reduction in the number of weekly FI episodes (from 5 ±2 to 3 ±2, $P=0.029$), however the change in their Wexner Incontinence scores (13 ±2 to 12 ±4; $P=0.766$) was only marginal.

The median duration of the temporary stimulation in the whole cohort was 21 days (range 8-23); this did not differ between responders (21 days, 15-23) and non responders (21 days, 8-22) ($P=0.899$, Mann Whitney) *(Table 7.1).*

Table 7.1 – Demographics and Clinical data:

	Responders n=16	Non-responders n=7	P value
Sex	16 f	6 f, 1 m	0.664 ‡
Age	48.5 (37-72)	50 (30-77)	0.910 †
Aetiology of FI			0.078 ‡
Obstetric	10	2	
Idiopathic	1	4	
Post-pelvic surgery	2	0	
Sphincter atrophy	1	0	
Scleroderma	1	0	
Subarachnoid haemorrhage	1	0	
Rectal prolapse	0	1	
Baseline Wexner scores	14.1 ± 3.1	13.1 ± 2.1	0.483 §
EAUS results			0.532 ‡
Intact	9	4	
Atrophy	2	2	
Defects	5	1	
Duration of stimulation	21 (15-23)	21 (8-22)	0.899 †
Follow up Wexner scores	6.3 ± 4.4	12.7 ± 3.5	**0.0073** §

† Mann Whitney U test
‡ Chi-Square test
§ un-paired *t* test

7.4.2 Anal manometry

Maximal Squeeze pressure significantly increased with stimulation; from 40 (6-156) cmH2O to 65 (16-243) cmH2O (P=0.0003). No significant increase in the resting pressure was demonstrated *(Table 7.2)*. However, subgroup analysis revealed that resting pressures significantly improved in responders.

7.4.3 Rectal compliance

Median baseline rectal compliance [11.5 (7.9-21.8) ml/mmHg] didn't significantly change following temporary SNS [12.4 (6.2-22) ml/mmHg, P=0.941]. This was also the case when examining responders and nonresponders separately *(Figure 7.1 and Table 7.2)*.

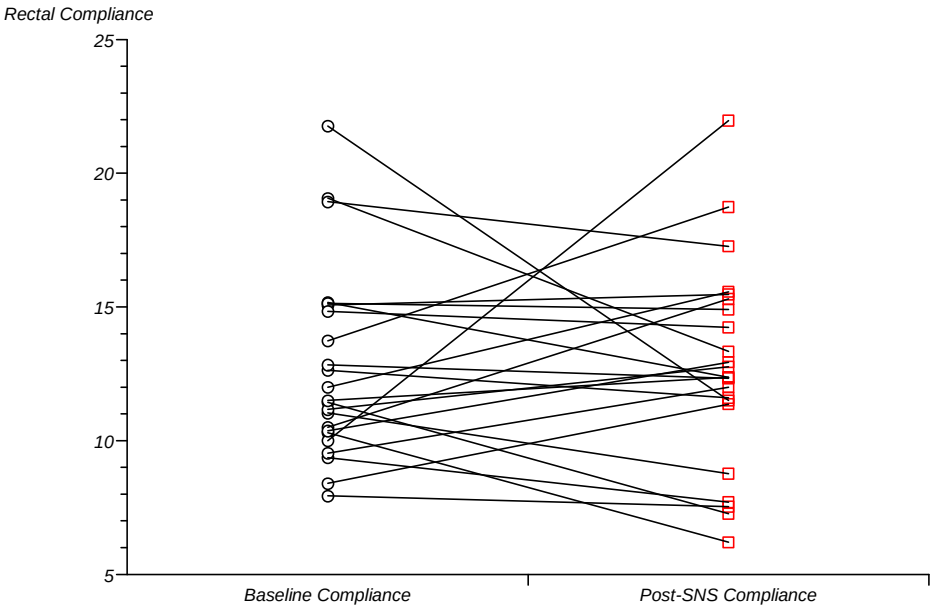


Figure 7.1 – Ladder plot demonstrating changes in rectal compliance following SNS

Table 7.2 – Anal Manometry and Rectal Compliance results:

	Baseline *	Post-stimulation *	P value §
Resting Pressure (cmH2O):			
All (n=23)	40 (16-113)	52 (16-119)	0.098
Responders (n=16)	39.5 (16-77)	50 (22-97)	0.051
Non-responders (n=7)	58 (18-113)	52 (16-119)	0.813
Squeeze Pressure (cmH2O):			
All (n=23)	40 (6-156)	65 (16-243)	**0.0003**
Responders (n=16)	50 (14-156)	75.5 (25-243)	**0.010**
Non-responders (n=7)	31 (6-142)	46 (16-185)	**0.016**
Rectal Compliance (ml/mmHg):			
All (n=23)	11.5 (7.9-21.8)	12.4 (6.2-22)	0.941
Responders (n=16)	11.7 (7.9-19.1)	12.4 (6.2-22)	0.782
Non-responders (n=7)	13.7 (9.4-21.8)	12.8 (7.7-18.8)	0.469

* data presented as median (range)
§ Wilcoxon Ranks

7.4.4 Rectal sensory thresholds

7.4.4.1 Distension thresholds

Maximal Tolerated Volumes (MTV) increased following stimulation. Additionally, pressures associated with Urgency (U press) and Maximal Tolerated distension (MT press) were significantly increased. In the Non-Responders (n=6), this pattern of change in pressures was not seen *(Table 7.3)*. There was no significant change in First Sensation (FS) volumes or pressures or Urgency volumes.

7.4.4.2 Electric sensory thresholds

There was no change in electric sensory thresholds following temporary SNS *(Table 7.3)*.

Table 7.3 – Rectal sensory thresholds:

		Baseline *	Post-stimulation *	P value §
FS Vol † (ml)	All (n=22)	66.5 (25-160)	71 (23-160)	0.949
	Responders (n=16)	83.5 (25-160)	82 (23-160)	0.706
	Non-responders (n=6)	60.5 (29-100)	53 (31-104)	0.844
U Vol † (ml)	All (n=22)	131 (50-236)	144 (30-299)	0.658
	Responders (n=16)	141.5 (50-236)	150 (30-299)	0.719
	Non-responders (n=6)	114.5 (77-150)	117 (70-149)	0.688
MTV Vol † (ml)	All (n=22)	175 (70-271)	199.5 (60-307)	**0.043**
	Responders (n=16)	185 (70-271)	210 (60-307)	0.144
	Non-responders (n=6)	150 (120-240)	176 (145-265)	0.094
FS Press † (mmHg)	All (n=22)	11 (7-23.1)	11.1 (6.4-22.9)	0.832
	Responders (n=16)	10.9 (7-23.1)	11 (6.4-22.9)	>0.999
	Non-responders (n=6)	14.6 (7.2-20)	13 (7.1-20.1)	0.625
U Press † (mmHg)	All (n=22)	15.4 (11-26.7)	19 (11.1-42.7)	0.054
	Responders (n=16)	15.3 (11-26.7)	19 (11.1-42.7)	0.08
	Non-responders (n=6)	19.1 (11.3-24.1)	19.2 (14.6-27)	0.625
MT Press † (mmHg)	All (n=22)	21.6 (8.5-31.9)	27.1 (14.3-43.3)	**0.023**
	Responders (n=16)	20.6 (8.5-31.8)	27.1 (14.3-43.3)	0.058
	Non-responders (n=6)	23.4 (14.9-31.9)	25 (19-38.8)	0.313
Electric thresholds (mA)	All (n=23)	20 (12-36.5)	23 (9.5-40)	0.903
	Responders (n=16)	20.3 (12-28)	23 (9.5-34.5)	0.831
	Non-responders (n=7)	19.5 (16-36.5)	23 (19.5-40)	>0.999

* data presented as median (range)
§ Wilcoxon Ranks
† data of a non-responder was excluded because of hindgut denervation

7.4.5 Rectal Doppler Mucosal Blood Flow results

There was a slight reduction in the Doppler Mucosal Blood Flow readings following stimulation but the magnitude of this did not reach statistical significance *(Table 7.4)*.

Table 7.4 – Doppler Rectal Mucosal Blood Flow:

	Baseline *	Post-stimulation *	P value §
All patients (n=23)	125.8 (69.9-346.8)	112.4 (50.2-404.1)	0.735
Responders (n=16)	125.4 (69.9-346.8)	113 (89.2-404.1)	>0.999
Non-responders (n=7)	150.8 (85.5-205.6)	111.8 (50.2-156.9)	0.75

* data presented as median (range)
§ Wilcoxon Ranks

7.5 Discussion

7.5.1 Principal findings and comparison with the findings in the literature

The results of this study demonstrate changes to rectal sensory function following temporary SNS. The maximal tolerated volumes were increased after SNS; additionally I have also demonstrated an increase in the rectal pressures associated with urgency and maximally tolerated distension. Such changes are thought to be mediated via autonomic pathways and might be indicative of changes in rectal wall tension and up-regulation of mechanoreceptors in the pelvic floor.

However, the study demonstrates that stimulation is not associated with a change in rectal compliance. Moreover, in this study, RDMBF did not significantly change when measured after the period of temporary stimulation in contrast to what was shown by Kenefick et al [122].

Although some studies have shown no change in anal pressures with SNS [98, 99, 106, 120], the majority have demonstrated an increase in the sphincter squeeze pressure with stimulation [76, 77, 79, 92, 97, 116-118]. In this study I have demonstrated changes in voluntary squeeze pressure in all patients. As such, this study is in agreement with the majority of the physiological data, suggesting that there is a motor outcome following SNS. However, the elevation of pressures in both Responders and Non-Responders suggests that this mechanism may not be central to its therapeutic benefit. Effects on the resting sphincter pressure, which is mainly under tonic autonomic control, were less clear. This study has suggested that only in Responders there was an increase in resting sphincter pressure.

The identified anorectal physiological changes following temporary SNS according to this study can be summarised in the following points:

- Increased maximal tolerated volume
- Increased rectal pressures associated with Urgency and Maximal distension Increased anal squeeze pressures
- Increased anal resting pressures (in responders only)

Although this study did not demonstrate a change in rectal compliance following temporary SNS, the changes demonstrated in rectal pressures and rectal sensory thresholds together with the changes in resting pressures in the subgroup of responders strongly suggest that SNS does selectively influence the anorectal autonomic nervous pathway.

Although this is an indirect evidence for the process of neuromodulation as the underlying mechanism in SNS; it strongly supports the landmark study of the latency of the sphincter response to acute stimulation of the sacral nerves, in which Fowler et al demonstrated that it was much longer than would be expect if it was the mere result of direct stimulation of the efferent motor fibres, suggesting a complex multisynaptic pathway [113].

The influence of SNS on the autonomic nervous system appears to be selective and remains unclear. For instance, the autonomic system does alter rectal motility and tone which are aspects closely linked to rectal compliance; nevertheless, there was no change in rectal compliance following SNS. This was in agreement with three studies which have examined rectal compliance with SNS [108, 118, 120]. Moreover, in this study RDMBF did not significantly change when measured after the period of temporary stimulation in contrast to what was previously shown by Kenefick et al [122].

This could be a result of the current settings that are in use in SNS. Different types of nerve fibres have different thresholds of stimulation by electric current, and therefore it might be that at the currently used sub-threshold stimulation the autonomic nerves are not fully recruited by SNS. The C fibres which are responsible for pain have the highest threshold of stimulation; and it might be necessary to ensure that patients have a good degree of awareness of the stimulation or even slight pain with it to ensure full recruitment and involvement of the mixed sacral nerves in the process of SNS.

The changes in rectal sensory distension thresholds demonstrated in this study are unique and are in agreement with only one study in the literature[118]. Most studies have demonstrated either no change in thresholds or a decrease in the distension thresholds *(see Table 3.3)*. This significant inconsistence could be due to the utilisation by different authors of significantly different methodologies when assessing rectal sensory thresholds. Most studies utilise the rectal balloon and only few authors have used the rectal barostat in assessment of rectal distension thresholds. The methodology used by Michelsen et al[118] was very similar to the one I utilised in this study. Some feel that the most important distension threshold is the 'First Sensation' and that the rest are subjective points; as very small 'First Sensation' volumes can be associated with significant urgency symptoms and urge faecal incontinence. The study demonstrated no significant changes in the 'First Sensation', however, the changes identified in the MTV and rectal wall pressures point to certain physiological changes which shed light on potential mechanistic changes.

7.5.2 Strengths and limitations of the study

Only few studies have examined rectal compliance with SNS and only three have used the more accurate method of the electromechanical barostat device[108, 118, 120]. I used this technique which has been shown to have good day-to-day and centre-to-centre reproducibility for measurement of rectal compliance[44, 153, 154].

Although the aetiology of incontinence in the cohort of patients in this study is diverse they represented a homogenous similar symptom profile, and reflected "real life" practice. It is possible that the different aetiologies might influence baseline physiological parameters and hence the putative effects of SNS. For obvious reasons the effects of SNS cannot be studied on healthy controls. However, Morren et al[115]examined the effects of an electric current generated over the sacrum using a magnetic field in healthy controls, individuals with faecal incontinence and spinal injury patients on anorectal physiology. They demonstrated an increase in anal pressures in all controls but failure to provoke such an increase occurred in a quarter of the FI patients, raising the possibility that destruction of certain neuronal pathways in those patients made the stimulation unsuccessful.

Another limitation of this study is that the subject numbers are low. Inevitably, therefore, we cannot exclude the fact that some of the changes seen may reflect a type-II statistical error. The fact that the majority of individuals respond to temporary stimulation means that comparison between such Non-Responders and Responders is even more problematic.

7.5.3 Clinical implications

The study suggests that anorectal autonomic function is selectively influenced by SNS. Some of the changes identified were more evident in responders; although small numbers make the interpretation of these findings only primitive. This could eventually

lead, especially when utilising the newly available methods to accurately assess the anorectal physiology are utilised, to the isolation of a physiological marker of response to stimulation.

The current lack of a definite physiological marker of response to temporary stimulation means that the assessment of response remains based merely on change in symptoms, a process which although widely used clinically is potentially associated with error and subjectivity. This general inability to identify a consistent physiological marker of a specific mechanism of action could raise the possibility of a mainly placebo effect associated with successful SNS. Alternatively, this may reflect an inadequacy of the tools available in studying anorectal physiological changes. The recent technological developments introducing high resolution manometry techniques and detailed functional imaging might change this in the near future.

7.5.4 Future research

This study will inform a larger long-term study. This will address both the persistence of SNS-induced changes with time, as well as the issue surrounding study group size. Such studies of chronic stimulation are much needed, especially since the reported discrepancy between rates of clinical success with temporary and permanent SNS[92] might suggest that there is a difference in the underlying mechanisms involved during each stage. Long term studies, however, might reveal that such discrepancy might just

be the result of an erroneous over-selection of responders following the temporary phase.

Studies of the physiological changes with SNS utilising the new technology of High Resolution Manometry is warranted. This technology yields significantly more information on the function of the anorectum and therefore it can potentially capture certain physiological changes that occur during SNS but are currently missed due to the lack of ability to record them.

7.5.5 Conclusions

I demonstrated in this study that there are some changes in the anorectal autonomic function; however, this was found to be rather selective. As we understand the threshold of different nerve fibres to electric stimulation are variable (from lowest to highest: sensory fibres, somatic motor fibres, afferent fibres, autonomic fibres then pain fibres). I propose that we should study the anorectal physiological changes and rectal compliance following acute stimulation of the sacral nerves under general anaesthesia. This will enable us to examine the effects on rectal compliance whilst increasing the level of stimulation to high levels which ensure the recruitment of the myelinated autonomic fibres. Additionally, I propose that we should study and compare the anorectal physiological changes associated with different SNS using different settings of current amplitude, threshold and frequency. All studies to date have only used the standard

historical settings which are still in use since the initial work conducted by the urologists.

Chapter 8

Blinded examination of effects of acute alteration of stimulation (ON/OFF) on anal manometry during temporary SNS

8.1 Chapter layout

In this chapter, I present the findings of the second study of the project which focused on examination of the changes in anal pressures on acute alteration of the device settings. An introduction to the study is presented, followed by description of the methodology, results and discussion.

8.2 Specific study rationale

Following the examination of the cumulative effects of temporary SNS on anal manometry and rectal physiological properties (presented in Chapter 7), I planned to examine the effects of acute alteration of the status of stimulation during the temporary phase (ON and OFF) on anal pressures. The aim of this experiment was to establish the nature of the underlying mechanistic process behind the physiological effects seen with SNS. I hypothesised that the acute alteration of SNS status will not have an effect on the anal pressures measured, as I propose that the changes in anal pressures are only a manifestation of a more complex process of neuromodulation rather than a result of direct efferent stimulation.

Most studies examining physiological parameters with SNS have assessed changes occurring following a period of stimulation compared to baseline values. In clinical practice, it is noted that changes in symptoms following stimulation are usually gradual

and often with evidence of some carry-on effect; however, the extent of acute physiological change with acute alteration of settings requires further investigation.

Some authors have recorded transient physiological changes with stimulation. Vaizey et al demonstrated an increase in rectal compliance when measured 24 hours after the onset of stimulation but returning to baseline levels when measured at day 7 [77]. Similarly, Leroi et al demonstrated an increase in anal pressures with temporary stimulation which was not demonstrable with chronic stimulation [91].

Studies so far have not identified a detectable physiological marker of stimulation, something which can potentially be useful in assessing the response to the trial stimulation. The presence of a motor sphincteric or pelvic floor response during the insertion of the stimulation lead intra-operatively is not always predictive of a clinical response, albeit it is important in determining the correct placement of the electrode. Interestingly, however, a study has reported proceeding with permanent implantation based on the presence of a motor response intra-operatively in 16 patients (11 with neurogenic incontinence) with good clinical outcomes at mid-term follow up [97].

Few studies have attempted to examine physiological changes following acute alterations of stimulation settings. Kenefick et al [122] examined the effects of altering stimulation amplitude and status (ON/OFF) on Rectal Doppler Mucosal Blood Flow (RDMBF), showing significant rise of the flux relative to the amplitude of stimulation up to 1 Volt. However, other authors failed to demonstrate such a phenomenon [140]. In

addition to examining RDMBF, Dudding et al also examined effects of acute alterations on rectal compliance [140] showing an increase in compliance with the reduction in pulse width or the increase in pulse frequency. However, the details of order of these changes and the potential order effect on compliance measurement were not discussed. In this context, it is interesting that Chung et al have found similar results with experimental stimulation of the afferent dorsal nerve of the penis [139]. Nevertheless, I was discouraged from studying acute changes in rectal compliance as findings following few pilot cases were suggestive of a significant order effect when barostat rectal distensions are carried out in succession (the second measurement being always higher than the first).

Maintenance of continence involves a complex multitude of factors, involving not only the sensori-motor function of the anorectum but also overall colorectal motility, stool consistency and the overall subject's fitness and mobility. Nevertheless, normal sphincteric function is an important component of this equation.

Anal manometry is an important measurement which guides our understanding of the pathophysiology of functional anorectal disorders, and the measurement of resting and squeeze pressures have been proved to be highly reproducible in the same subject on separate days[153].Anal pressures reflect the state of sphincter function; what is believed to be the target end organ in this treatment modality.

It was initially believed that improvement of sphincter function with SNS could be related to a permanent training effect on the EAS, with stimulation-induced

transformation of fast twitch type II fatiguable muscle fibres to slow twitch type I fatigue-resistant fibres[76, 112]. However, later research showed significantly increased latency of the EAS contraction following to acute SNS intra-operatively, suggesting a reflexly induced afferent-mediated response [113].

Although, this neuromodulatory process is believed to be underpinning the positive clinical changes associated with SNS, further study to determine the exact associated physiological changes at the peripheral level is still required. This was the aim of this study which looks at changes to anal pressures following temporary stimulation and with acute alteration of stimulation settings.

Neuromodulation is a term referring to the situation where an electrical activity in a neuronal pathway influences the activity in another through synaptic interactions. Although, it implies chronicity and a slowly mediated change, the presence of a physiological change with acute alterations of the settings is a plausible concept.

This is clearly the case intraoperatively when acute stimulation is associated with pelvic floor and EAS contraction, albeit with a long latency. This usually happens with a stimulation threshold that is well above the sensory threshold as the patient is anaesthetised. However, this study aimed to assess any changes on alteration of the stimulation settings around or sub- threshold level. The stimulation settings whilst the patient is awake are not associated with an externally detectable sphincter contraction as

usually patients will not tolerate current amplitudes which are significantly above the sensory threshold.

The effects of acute alteration of stimulation settings on anal manometry in this manner are not known as there are not such studies reported in the literature.

Clinical cross-over SNS studies[102, 103] conducted anorectal manometry measurements with each setting but this was performed at the end of each phase which lasted few weeks and so does not provide information on changes with acute alteration of settings.

8.3 Patients and methods

All patients undergoing temporary SNS were symptomatic for at least one year and had failed all conservative measures including dietary, pharmacological and biofeedback treatments. Routine pre-operative assessment included full clinical evaluation, anorectal physiological studies and endo-anal ultrasound. Weekly bowel diaries detailing the frequency of bowel movement, the episodes of incontinence and stool consistency and Wexner Incontinence Questionnaires were completed by the patient before and during the temporary stimulation phase. In agreement with most authors[76, 7779], a positive clinical response to stimulation was considered if there was at least 50% improvement in symptoms.

8.3.1 Study design

During their follow up visit at the end of the period of temporary stimulation, consenting patients underwent two sets of anal manometry.

Physiological testing was conducted following the assessment of the clinical response of the patient. Using sealed envelope randomisation, an assistant allocated the patient to one of two groups: Device ON then OFF (Group 1) or Device OFF then ON (Group 2).

The assistant then altered the device settings whilst the patient and investigator remained blinded. However, when the device was set to ON, it was set to the level at which the patient had been receiving the stimulation and so complete blindness of the patients was not guaranteed as this level was usually at or just below sensory threshold. A few minutes were always left between changing the settings and commencement of the physiological measurements. The diagram in Figure 8.1 summarises the study design.

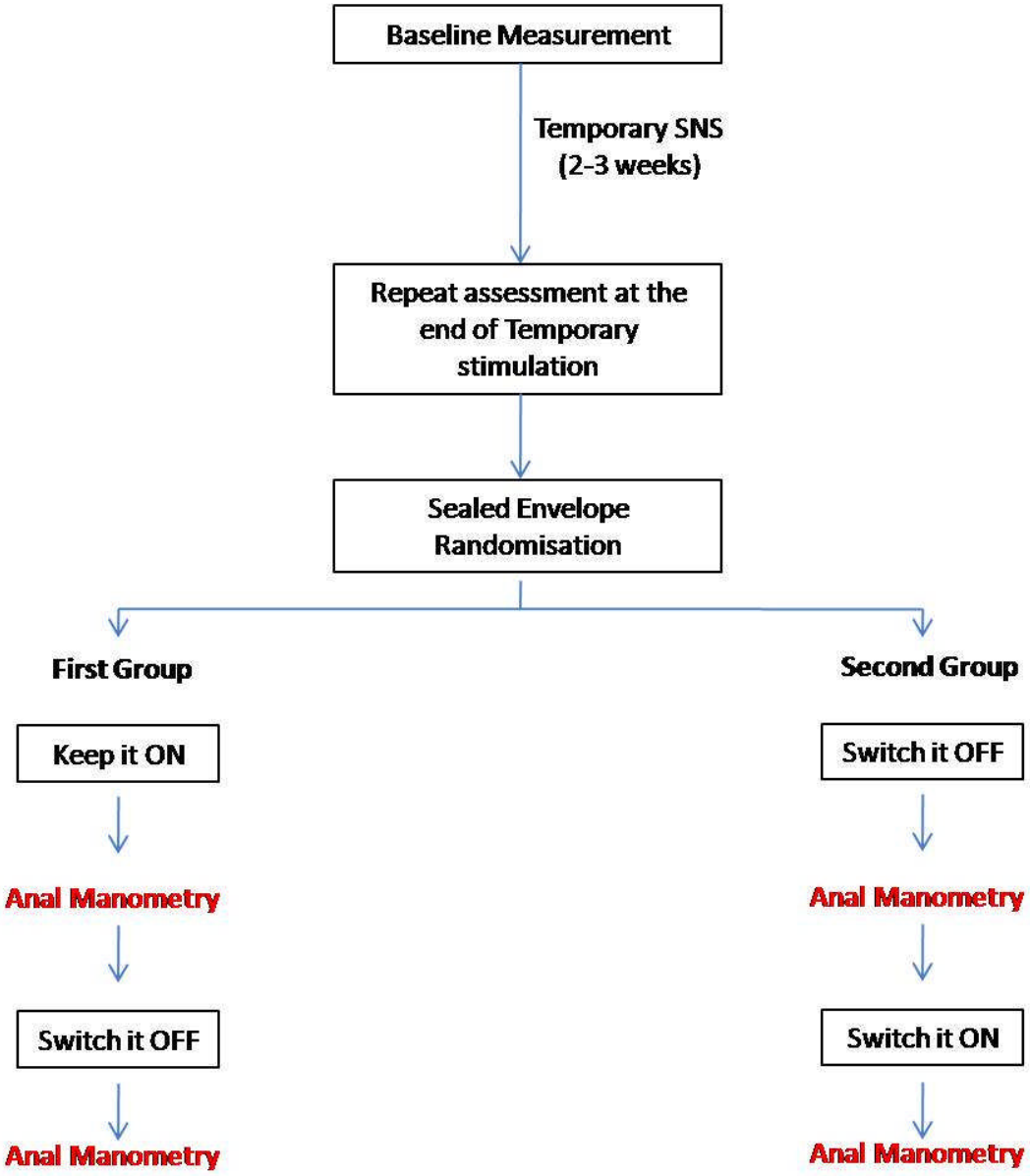


Figure 8.1 – Diagrammatic representation of the design of Study 2

8.3.2 Manometry technique

See Chapter 5 for details of manometry technique used. The catheter was completely withdrawn and kept perfused after the first manometry measurement. A two to four minutes' interval was left before re-introducing the catheter for the second manometry measurement.

8.3.3 Statistics

Statistical analysis was performed using *PASW® Statistics 18* software package, SPSS Inc, Chicago, Illinois, USA. Data was presented as mean with standard deviation or median and range according to their normality plots. Comparisons were made using the *t* test or Wilcoxon's signed ranks accordingly. A p value of 0.05 or less was considered statistically significant.

8.4 Results

Seventeen patients were successfully recruited to the study. Ten patients were randomised to Group 1 (ON then OFF) whilst seven were randomised to Group 2 (OFF then ON). The aim was for ten patients to be randomised to each group, but a mismatch was inevitable as only 17 patients were recruited.

8.4.1 Patients and clinical results

The demographics and clinical characteristics of this sub-cohort were similar to the overall study cohort described in chapter 6.

Fourteen patients (82%) had a favourable clinical response to temporary stimulation with an average reduction of weekly incontinence episodes from 3.9 ±2 to 1.2 ±1.9 (P=0.0001, *t* test) and their Wexner scores from 13.9 ±3.9 to 6.1 ±3.9 (P=0.0001, *t* test). SF-36 Quality of Life questionnaires demonstrated an improvement of quality of life but this was not statistically significant (baseline scores: 50.7 ±17.8, follow up scores: 60.9 ±22.9, P=0.154).

Table 8.1 – Clinical changes in responders and non-responders

	Baseline	Post- Stimulation	P value
Responders (n=14)			
Wexner Scores	13.9 ±3.9	6.1 ±3.9	0.0001
Incontinence episodes/week	3.9 ±2	1.2 ±1.9	0.0001
Non-Responders (n=3)			
Wexner Scores	15 ±3.6	13.3 ±6.4	0.549
Incontinence episodes/week	5 ±3.5	2.7 ±2.4	0.085

8.4.2 Anal manometry results

8.4.2.1 Resting pressure:

Resting pressure at the end of temporary stimulation did not significantly differ from baseline measurements. This was the case regardless of the status of stimulation (ON or OFF). The acute alteration of stimulation settings (ON to OFF in group 1 or OFF to ON in group 2) was not associated with significant change in the resting pressures. This was the case regardless of the order of change.

Table 8.2 – Results of resting pressures

			Parametric	Non Parametric
Baseline to first order	53.3 ±27.5 50 (16-113)	60.3 ±28.7 54 (26-119)	0.330 (paired t test)	0.492 (Wilcoxon's)
Baseline to ON	53.3 ±27.5 50 (16-113)	62.8 ±30 60 (22-119)	0.192 (paired t test)	0.246 (Wilcoxon's)
Baseline to OFF	53.3 ±27.5 50 (16-113)	65.7 ±28 64 (27-118)	0.116 (paired t test)	0.177 (Wilcoxon's)
Delta (ON minus Baseline) to Delta (OFF minus Baseline)	9.5 ±28.7 12 (-34 to 58)	12.4 ±30.8 11 (-33 to 75)	0.495 (paired t test)	0.378 (Wilcoxon's)
ON at the end of temporary stimulation to OFF at the end of temporary stimulation	62.8 ±30 60 (22-119)	65.7 ±28 64 (27-118)	0.495 (paired t test)	0.378 (Wilcoxon's)
Amount of change from ON to OFF compared to amount of change from OFF to ON	(n=10, Group 1) 9.2 ±15.2	(n=7, Group 2) 6 ±17.2	0.700 (independent t test)	-

8.4.2.2 Squeeze pressure

Squeeze pressures at the end of temporary stimulation were higher than baseline values. This was the case regardless of the status of stimulation (ON or OFF). The acute alteration of stimulation status was not associated with a change in the squeeze pressures.

Table 8.3 – Results of squeeze pressures

			Parametric	Non Parametric
Baseline to first order	68.2 ±48.3 40 (14-156)	97.7 ±63.6 80 (38-270)	**0.023** (paired t test)	**0.009** (Wilcoxon's)
Baseline to ON	68.2 ±48.3 40 (14-156)	91.8 ±56.6 80 (38-243)	0.060 (paired t test)	**0.036** (Wilcoxon's)
Baseline to OFF	68.2 ±48.3 40 (14-156)	92.8 ±63.6 60 (29-270)	**0.029** (paired t test)	**0.018** (Wilcoxon's)
Delta (ON minus Baseline) to Delta (OFF minus Baseline)	23.6 ±48.1 14 (-44 to 159)	24.6 ±42.1 10 (-29 to 129)	0.869 (paired t test)	0.378 (Wilcoxon's)
ON at the end of temporary stimulation to OFF at the end of temporary stimulation	91.8 ±56.6 80 (38-243)	92.8 ±63.6 60 (29-270)	0.869 (paired t test)	0.959 (Wilcoxon's)
Amount of change from ON to OFF compared to amount of change from OFF to ON	(n=10, Group 1) -8.3 (±24.7)	(n=7, Group 2) -14.3 (±18.9)	0.580 (independent t test)	-

8.5 Discussion

8.5.2 The principal findings and comparison with the literature

The study reveals no change in resting pressures, neither at the end of temporary stimulation nor with the acute alteration of device status (ON/OFF). This is in agreement with other authors who reported no change in resting pressures with stimulation[76, 77, 91,

[92, 98, 99, 106, 117, 120]. However, it creates ambiguity about the influence of SNS on the autonomic function of the anorectum; which what controls IAS function. Other studies have also shown no changes with stimulation in physiological parameters believed to be a manifestation of autonomic function in the anorectum namely RDMBF and rectal compliance[108, 118, 120, 140]. The influence of SNS on the autonomic function could be selective, or the fact that stimulation is carried at a sub-threshold level is leading to incomplete recruitment of the autonomic nerves.

The study demonstrates significant increase in the maximal squeeze pressures after the period of temporary stimulation, however, acute changes of ON to OFF or vice versa was not associated with a change. This suggests that the enhancement of the EAS function is an outcome of a cumulative chronic change over time rather than an acute process.

Squeeze pressure measurements are influenced by patient's level of cooperation and by muscle fatigue, and so it can be argued that this finding is not robust. However, the blinded design of this study and the fact that the increase was present whether the setting at first order was ON or OFF counters this argument. Nevertheless, as some have shown that intra-individual reproducibility when measuring squeeze pressures is very low[155], one might doubt the significance of the detected change in squeeze pressures. However, the consistent finding in seventeen patients reaching statistical significance argues strongly against such a suggestion.

In this thesis so far and in the general literature, the presence of increased squeeze pressures with SNS seems to be the main constant feature. This suggests that an improved function of the EAS neuromuscular unit is the sole function of SNS. This hypothesis, however, does not explain the other – albeit inconsistently – reported changes such as those in rectal sensory function or rectal compliance. It also does not explain the occasionally reported positive clinical results in conditions such as idiopathic chronic constipation.

I feel that although changes in EAS function seem to be the most consistent findings, the overall consideration of the evidence actually stands to suggest that SNS does work on multiple levels influencing all the peripheral nerve systems (somatic, motor and autonomic) and potentially via modulating the pathways to the CNS. I feel that the reason we cannot consistently demonstrate otherwise is that we yet do not have the efficient tools of detecting all the physiological changes occurring at the target organ.

8.5.3 Strengths of the study

This study is one of only few where physiological changes were studied whilst device settings are acutely altered. The examiner was blinded to the nature of the device status and therefore operator bias was not eliminated to great extent.

8.5.4 Shortcomings of the study

The study has a design problem as all patients were subjected to the ON/OFF experiment. It would have been more condusive to answering the research question if only those patients who demonstrated an increase in anal pressures following the period of temporary stimulation were selected for the study where an ON/OFF experiment is carried out.

It is to be mentioned also, that there was an imbalance in the group numbers. I aimed to recruit ten patients to each group, but with only seventeen recruits a slight imbalance of the numbers in each group was inevitable. This mild imbalance, however, is felt to have not significantly impacted the statistical analysis.

Moreover, patients' blinding was problematic. On randomisation between ON and OFF, the protocol was to use the patient's own settings and amplitude of stimulation when keeping or switching the device ON. This meant that for some patients the discrimination between ON and OFF was possible as some patients have the stimulation at or above threshold level. Nevertheless, the patient's settings were usually just sub-threshold and with the passage of time most patients report the loss of continuous awareness of stimulation. Patients during the study were not asked whether they can determine the status of the device settings during the experiment.

Anorectal manometry is a well established robust method for assessment of sphincter function. A number of studies have demonstrated its day-to-day reproducibility [153, 156]. Inter- and intraindividual reproducibility was also established for the measurements of resting pressure[155].

However, there is no doubt that SNS influences the whole pelvic floor which receives a significant part of its nerve supply with direct branches from S3 nerve root prior to its joining the pudendal nerve [111]. The ability of standard anorectal manometry in assessing the global pelvic floor function including puborectalis and the proximal sphincter function is not clear, and it might be that recent techniques like high resolution manometry (HRM) are better suited to this role[40].

Chapter 9

Effects on the Recto-Anal Inhibitory Reflex

9.1 Chapter layout

In this chapter, I present the findings of the third study of the project which focused on examination of the changes in the Recto-Anal Inhibitory Reflex following temporary SNS. An introduction to the study is presented, followed by description of the methodology, results and discussion.

9.2 Specific study rationale

In the course of investigation of potential SNS mechanisms in faecal incontinence and following the study of rectal compliance and anal pressures, I decided to examine the potential changes mediated through intrinsic enteric nervous pathways. One of the manifestations of this intrinsic neuronal system is the Recto-Anal Inhibitory Reflex (RAIR); and therefore I aimed in this study to examine the RAIR parameters before and after SNS.

The Recto-Anal Inhibitory Reflex (RAIR) is a reflex relaxation of the proximal internal sphincter in response to sudden rectal distension. This is an ongoing phenomenon which occurs on a regular basis (few times per minute) and allows the delivery of the newly arrived rectal contents to the lower anal canal where the specialised sensory mucosa can establish its nature[157]. The contents are delivered back to the rectum by the effect of the high pressure generated by the presence of the external sphincter overlapping the lower

anal canal. Figure 5.12 demonstrates the various parameters of RAIR as seen on a manometry trace.

The RAIR was first described by Gowers in 1877[158] and was later confirmed in 1935 by Denny-Brown and Robertson [157]. The reflex is thought to be mediated via the intramural neuronal plexus [137], and its absence is used as a diagnostic criterion for Hirschsprung's disease [159, 160]. The reflex is also absent following rectal resections, however there is some evidence that it recovers with time[161].

RAIR is – therefore – an important component of the continence mechanism and anorectal function, and some authors have suggested that certain changes to this reflex can be associated with disturbed continence. Some investigators have examined the RAIR parameters in patients with different anorectal disorders and in control subjects. Kaur et al [162] showed significantly greater sphincter relaxation in the incontinent as compared with the constipated and control subjects. They however reported no difference in the reflex Latency or Total Duration between the groups. In another study, Eyers and Thomson showed that the internal sphincter relaxes more readily in response to rectal balloon distension in patients with idiopathic pruritus ani compared to their control subjects [163]. Farouk et al showed similar results from ambulatory monitoring in patients with the same condition [164]. This collectively suggests that altered responses of the internal anal sphincter to rectal distension play a role in the pathophysiology of disordered continence.

Most studies which have attempted to examine the anorectal physiological changes with SNS have only reported the presence or absence of the reflex. No study in the context of SNS has attempted to examine potential changes in RAIR parameters. Altomare et al [98] examined anal manometry before and after permanent SNS implantation in 14 patients and reported a slight reduction in the volume required to elicit the reflex following SNS.

The aim of this component of my thesis was to study the RAIR parameters before and at the end of temporary SNS. RAIR is believed to be mediated via the intrinsic neuronal pathways (the myenteric and submucosal plexi); however, these intrinsic pathways are potentially influenced by autonomic control. I hypothesised that RAIR parameters will be changed followed SNS. As the previous studies in this body of work have revealed evidence of potential changes in the autonomic anorectal functions secondary to SNS, I proposed that a potential manifestation of this change could be a change to the RAIR with resultant enhanced reflex relaxation and optimisation of the 'Sampling' process. Additionally, the influence of SNS on the mixed sacral nerves is potentially associated with changes in the intrinsic pathways through synaptic interaction; the exact concept of neuromodulation which is the change in one neuronal pathway as a result of stimulation of another.

9.3 Patients and methods

9.3.1 Patients and clinical assessment

A cohort from the main study population was recruited. All patients were symptomatic for at least one year and had failed all conservative measures including dietary, pharmacological and biofeedback treatments. Routine pre-operative assessment included full clinical evaluation, anorectal physiology studies and endo-anal ultrasound.

Weekly bowel diaries detailing the frequency of bowel movements, the episodes of incontinence and stool consistency and Wexner Incontinence Questionnaires were completed by patients before and during the temporary stimulation phase.

9.3.2 Study design

All study subjects underwent full anal manometry including RAIR testing before and at the end of temporary SNS. In seven patients, the RAIR was tested twice at the follow up stage (i.e. at the end of temporary SNS): a) with the device ON and then b) with the device OFF, to assess any potential change with acute alteration of stimulation status. In this cohort, the follow up values for comparison with pre-stimulation baseline findings were chosen as those recorded whilst the device was ON.

9.3.3 Anal manometry and RAIR methodology

Detailed description of methodology is mentioned in Chapter 5.

9.3.4 Statistical methods

Statistical analysis was performed using PASW Statistics 18 software package, SPSS Inc, Chicago, Illinois, USA. Data was presented as mean with standard deviation or median and range according to their distribution. Comparisons were made using the *t* test or Wilcoxon's signed ranks accordingly. P values of 0.05 or less were considered statistically significant.

9.4 Results

Fourteen patients (13 Female) from the main project population undergoing temporary SNS for intractable FI were recruited to the study.

9.4.1 Patients and clinical outcomes

The demographics and clinical characteristics of the recruited patients were similar to those of the main cohort described in Chapter 6.

The mean duration of temporary stimulation in this cohort of patients was 19 (±4) days. Eight patients (57.1%) had a favourable clinical response to stimulation with an average reduction of weekly incontinence episodes from 5 ±2.6 to 1.4 ±2.8 (P=0.022, t-test). Wexner scores in this group also significantly reduced from 13.9 ±2 to 5.9 ±4 (P=0.0001, t-test). Non-Responders experienced some reduction in the number of weekly incontinence episodes (from 6.4 ±1.4 to 3.7 ±2; P=0.048), however, their overall Wexner scores did not significantly improve *(Table 9.1)*.

SF-36 Quality-of-Life Questionnaires captured some improvement in quality of life in Responders; however this was not statistically significant. It was also noted that the baseline SF-36 scores in Non-Responders were lower than in Responders (26 ±13.7 vs. 39 ±14.5), however, this was not statistically significant (P=0.179) *(Table 9.1)*.

Table 9.1 – Clinical outcomes:

	Baseline n=14	Post-SNS n=14	P value
Responders (n=8)			
Wexner scores	14 ±2	6 ±4	**0.0001**(t-test)
Incontinence episodes/week	5 ±2.6	1.4 ±2.8	**0.022**(t-test)
SF-36	39 ±14.5	55 ±23.6	0.069 (t-test)
Non-Responders (n=6)			
Wexner scores	15 ±4	16 ±2.6	0.314 (t-test)
Incontinence episodes/week	6.4 ±1.4	3.7 ±2	**0.048** (t-test)
SF-36	26 ±13.7	27.2 ±12.5	0.687 (t-test)

9.4.2 Physiological results

9.4.2.1 Anal pressures

In this cohort, squeeze pressures increased slightly with stimulation but there was no significant change in resting pressures *(Table 9.2)*.

9.4.2.2 Rectal compliance and rectal sensory thresholds

Rectal compliance did not significantly change with stimulation. Maximal Tolerated Volumes (MTV) showed a trend for an increase following SNS; however, this was not statistically significant. Other rectal sensory thresholds did not significantly change with stimulation *(Table 9.2)*.

Table 9.2 – Manometry, rectal compliance and rectal sensory thresholds:

	Baseline (n=14)	**Post-SNS (n=14)**	**P value**
Resting pressure	62 (32-100)	62 (21-119)	0.900 †
Squeeze pressure	36 (26-101)	50 (8-185)	0.059 †
Rectal Compliance	12.3 ±2.1 12 (9.5-15.1)	13.7 ±2.9 13.6 (8.8-18.8)	0.139 ‡ 0.148 †
T volume	57.3 ±32.5 52 (20-105)	58.4 ±26 60 (20-104)	0.914 ‡ 0.898 †
U volume	101.5 ±41.4 100 (30-166)	124.2 ±43.8 118 (60-228)	0.244 ‡ 0.32 †
MTV volume	143.5 ±56 136 (40-240)	180.8 ±50.3 174 (110-265)	0.083 ‡ 0.102 †

† Wilcoxon signed ranks
‡ Paired *t* test

9.4.2.3 RAIR parameters (baseline versus post-SNS)

Assessment of all RAIR parameters revealed that the duration of Recovery Time significantly reduced with temporary SNS. This was associated with a significant reduction of the Total Reflex Duration *(Table 9.3 and Figure 9.1)*.

Table 9.3– RAIR parameters (baseline and post-SNS)

	Baseline (n=14)	Post-SNS (n=14)	P value
Excitation Latency (sec)	1.4 (±1) 1.2 (0.3-4.3)	1.7 (±1.3) 1.3 (0.4-5.4)	0.164 (t-test) 0.187 (Wilcoxon's)
Amplitude of relaxation (cmH2O)	35.9 (±13.2) 36.5 (13-55)	32.1 (±18.7) 32 (5-74)	0.555 (t-test) 0.530 (Wilcoxon's)
Percentage of the reduction (%)	53.4 (±14.8) 53.5 (20.3-71.1)	47.7 (±18.4) 47.1 (22-77.1)	0.359 (t-test) 0.638 (Wilcoxon's)
Recovery Time (sec)	7 (±4.5) 6.7 (1-13.7)	4.4 (±2.6) 3.7 (1.6-10.3)	**0.022** (t-test) **0.030** (Wilcoxon's)
Total Reflex Duration (sec)	13.8 (±6.4) 13.6 (5-26.8)	10.4 (±3.8) 9.6 (5.6-19.9)	**0.057** (t-test) **0.039** (Wilcoxon's)

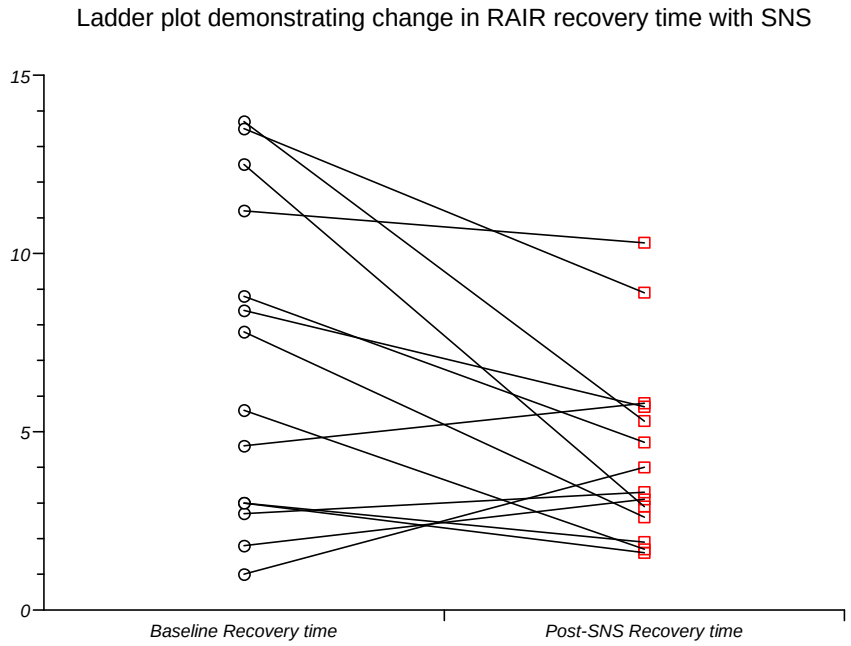


Figure 9.1 – Ladder plot demonstrating changes in RAIR recovery time following SNS

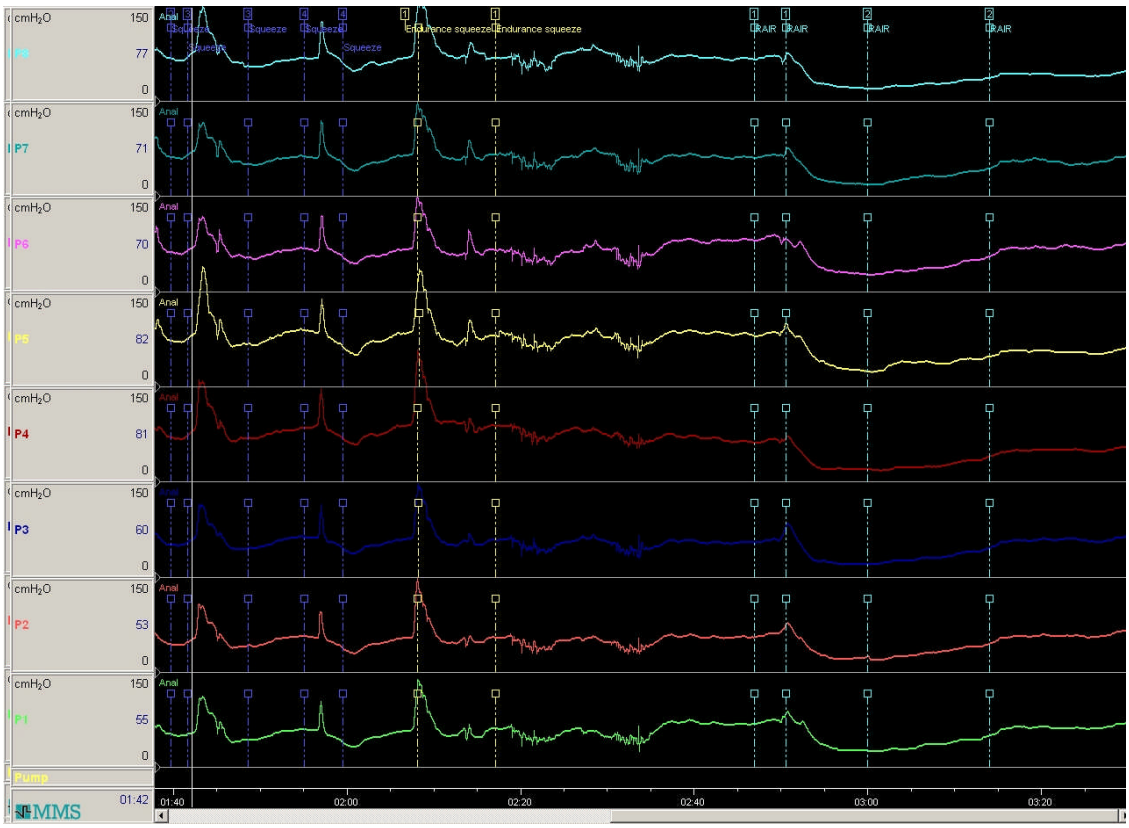


Figure 9.2 – Manometry trace demonstrating baseline RAIR trace

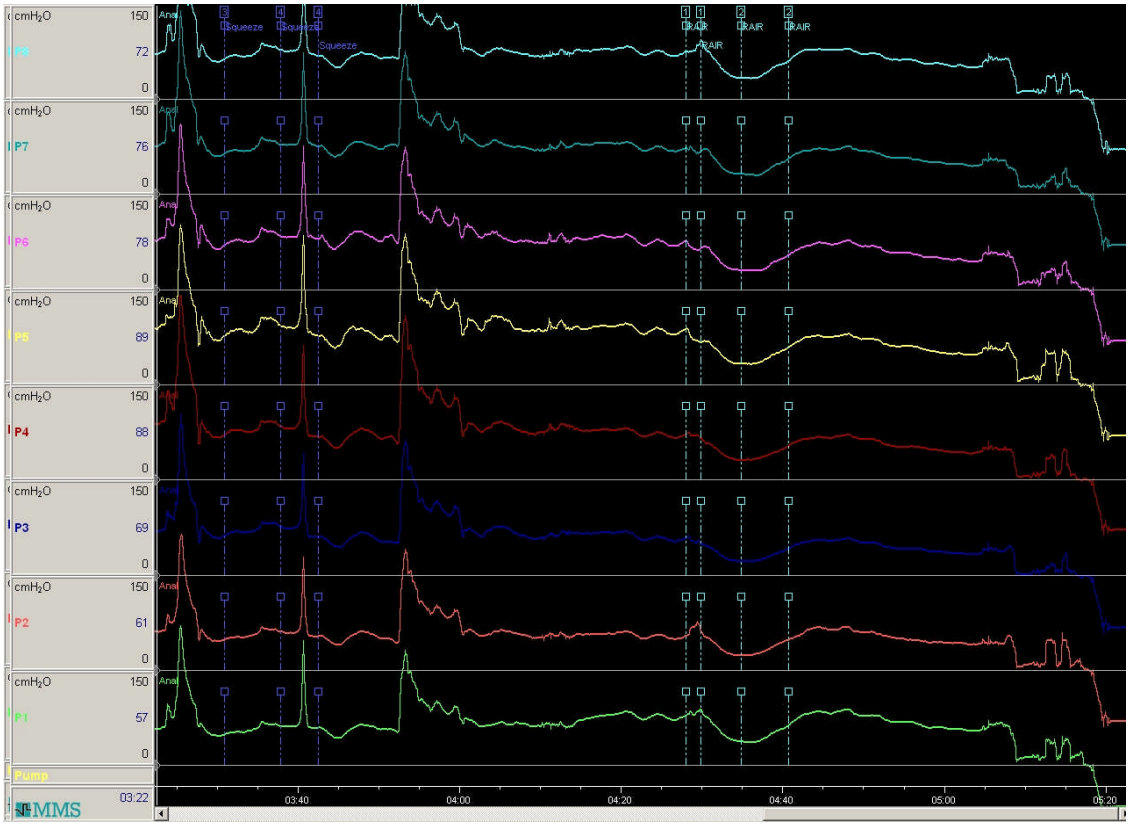


Figure 9.3 – Manometry trace demonstrating post-SNS RAIR trace (same patient in Fig 8.4)

9.4.2.4 RAIR parameters (acute ON/OFF change)

The acute alteration of device settings (ON and OFF) on testing at follow up was not associated with significant changes to any of the RAIR measured parameters *(Table 9.4)*.

Table 9.4 – RAIR parameters with ON/OFF alteration of the device at follow up testing:

	ON (n=7)	OFF (n=7)	P value
Excitation Latency (sec)	1.9 (±1.7) 1.4 (0.4-5.4)	1.4 (±1) 0.8 (0.6-3.1)	0.462 (t-test) 0.398 (Wilcoxon's)
Amplitude of relaxation (cmH2O)	32.3 (±16.3) 31 (8-57)	30.4 (±19.6) 29 (10-65)	0.691 (t-test) 0.672 (Wilcoxon's)
Percentage of the reduction (%)	45.1 (±18.1) 48.2 (22-64.8)	40.9 (±21.5) 38.2 (10.8-73.9)	0.507 (t-test) 0.499 (Wilcoxon's)
Recovery Time (sec)	3.8 (±2.2) 2.9 (1.7-7.7)	4.2 (±1.7) 3.8 (2.6-7)	0.653 (t-test) 0.310 (Wilcoxon's)
Total Reflex Duration (sec)	9.1 (±2.5) 8.7 (5.6-11.7)	11.1 (±5.1) 9 (7.1-20.7)	0.340 (t-test) 0.463 (Wilcoxon's)

9.5 Discussion

9.5.1 Principal findings and reflection of potential explanations

This study reveals significant reduction of the RAIR's Recovery Time following the period of temporary SNS. This was associated with subsequent shortening of the total reflex duration. This reduction in the duration of recovery of internal sphincter relaxation which results from rectal distension might be an important underlying mechanism in improving faecal incontinence, as the enhanced recovery of the sphincter could be instrumental in preventing unwanted episodes of incontinence that otherwise could have been precipitated by the regular occurrence of the sampling reflex, especially in those patients who often have dysfunctional external sphincters secondary to previous tearing or atrophy.

It is difficult to definitively explain the findings of the study from a mechanistic point of view; however, recovery of the internal sphincter during the RAIR is influenced by both neuronal and muscular factors. On the contrary, the latency of the reflex and its amplitude are influenced by purely neuronal or purely muscular factors respectively.

Therefore, it is likely that the influence of SNS on the sacral autonomic nervous system has a role to play in this change in the RAIR. It potentially leads to enhanced parasympathetic input to the internal sphincter leading to its quicker relaxation in response to the rectal distension and therefore a quicker return to its normal baseline

tone. However, the shorter recovery could be a result of enhanced sympathetic tone to the internal sphincter and increased baseline tone which causes the return of the pressure to the baseline value following the reflex relaxation to be quicker. The evidence of potential increase in the resting pressures in responders found in Chapter 6 study might be suggestive of this explanation.

However, it is believed that RAIR is mainly an intrinsic-mediated reflex. Experimental studies have demonstrated that RAIR is present after presacral nerve blockade and after full surgical mobilization of the rectum but is abolished by circumferential rectal myotomy [137]. The changes mediated by SNS are possibly fully mediated through the intrinsic pathways.

Nevertheless, on another level, Azpiroz et al[165] and Eckardt et al[166] observed that EAS contraction can reduce the IAS relaxation at RAIR. As demonstrated before, SNS is associated with an increased squeeze function and this enhanced EAS function could be resulting in a reduced reflex IAS relaxation during the RAIR and therefore a shorter recovery time.

Changes in RAIR Recovery Time could result from different positioning of the manometry catheter within the anal canal. Zbar[167] and Goes et al [168] demonstrated differential recovery times between the proximal and the distal portions of the sphincter. This is a potential confounding factor when the results of this study are interpreted. However, the consistency in the adopted technique was instrumental in ensuring that the

findings are truly representative of changes occurring over time rather than secondary to differential positioning of the manometry catheter. Moreover, the similarity of the resting pressures before and after stimulation suggests that differential catheter positioning did not occur.

In an important study of constipated, incontinent and control subjects, Kaur et al demonstrated significantly greater sphincter relaxation in the incontinent as compared with the constipated group [162]. This research did not demonstrate significant reduction in the amplitude of relaxation following SNS, but it did show a significant reduction in the recovery time of the sphincter which effectively will be associated with less sphincter relaxation. This change effected by SNS can therefore be viewed as a reversal of what is observed to be different in incontinent patient and is potentially a mechanistic change.

It has been also suggested that rectal sensory properties and compliance are factors which potentially influence the RAIR parameters[167]. However, in this cohort of patients rectal compliance did not change with SNS. Similarly, apart from tendency of increased MTV with stimulation, rectal properties on the whole did not change. This makes it unlikely that potential changes in rectal sensory function are the mediator of the RAIR changes observed with SNS.

In agreement with my findings regarding anal pressure changes with acute alteration of the device status, this study also demonstrate no acute change in RAIR parameters with the alteration of device settings (ON/OFF). The change in recovery time was only

demonstrated when compared with the baseline values. This further highlight the cumulative nature of SNS effects favouring the hypothesis that its mechanisms are neuromodulatory in nature.

9.5.2 Strengths of the study

The RAIR is an important component of the complex continence mechanism and a dysfunctional RAIR can be associated with symptoms of disordered continence [162-164]. Nevertheless, most anorectal physiological studies comment on the mere presence or absence of the RAIR, with only few investigators examining the details of RAIR parameters. As far as I am aware, no studies in the available English literature have examined the potential effects of SNS on the RAIR parameters making this study an important addition to the understanding of SNS mechanisms.

The technique of eliciting the RAIR can significantly alter the parameters of relaxation obtained. Monteiro et al and others have demonstrated that the parameters are significantly altered by the choice of inflation pattern[169, 170], with an increase in the length of IAS relaxation and the recovery time when sustained inflation is used instead of rapid inflation/deflation. Moreover, other investigators have demonstrated differential recovery times according to whether recording was made in the proximal or the distal sphincter [167, 168], with the RAIR being more a function of the proximal IAS sphincter [167].

In this study a standardized methodology was used to elicit the RAIR and was applied by one operator throughout the study. This involves the insertion of the manometry catheter which has a fixed volume balloon mounted at a fixed distance from the tip to the point where a stable manometry trace is obtained and rapid inflation/deflation was used. The manometry channels were designed circumferentially at the same level, and therefore only one segment of the internal sphincter in each patient was tested. Variations between the proximal and distal sphincters are therefore not captured.

9.5.3 Weaknesses of the study

Nevertheless, the study has its limitations as the number of subjects is relatively small. Furthermore, patients represent a tertiary centre practice and selection bias could be a problem. However, it is to be mentioned that patients in the study have on the whole represented a reasonably homogenous cohort of patients with regard to the aetiology and the clinical profile of their incontinence.

Another limitation of the study is that the operator was not blinded during the analysis of the data. However, the baseline and follow up data were not analysed in one session and not consecutively for each patient.

9.5.4 Implications and future research directions

This study further supports the argument that SNS effects include afferent-mediated and neuromodulatory mechanisms. The study population is small but an important finding is reported and further larger studies will be required to validate this research.

The mechanisms involved in modifying the RAIR function during SNS stimulation are likely to involve influences mediated through the autonomic nervous systems. Further research performing a similar study whilst pharmacologically obliterating the anorectal sympathetic and parasympathetic receptors respectively will be helpful to investigate this in further detail.

Furthermore, I propose the examination of RAIR changes during acute SNS stimulation at different current intensity under general anaesthesia (at the time of wire insertions). This will enable to examine the effect of recruiting all the peripheral nerves in the mixed sacral nerves which have different threshold to electric stimulation, not all of which are tolerated by the patients during the phase of temporary stimulation.

Chapter 10

Effects on rectal evacuatory and pelvic floor function:

Assessment using MR Proctography

10.1 Chapter layout

In this chapter, I present the findings of the fourth study of the project which focused on examination of changes to the pelvic floor function and structure following temporary SNS utilising dynamic MR technology. An introduction to the study is presented, followed by description of the methodology, results and discussion.

10.2 Specific study rationale

Although, neuromodulation is believed to be the underlying process by which changes in one neuronal pathway alter the activity in another through synaptic interaction[113]; the functional targets of SNS are not clearly identified. The current clinical practice involves selecting patients for permanent device implantation on the basis of their clinical response during a period of temporary stimulation. This process, nevertheless, can be a subjective one; with some evidence of discrepancy between the success rates of temporary and permanent stimulation[92].

I proposed that pelvic floor muscles (levator ani and puborectalis) are potential direct targets of SNS effects. This is based on the fact that the pelvic floor receives direct nerve supply from the third sacral nerve. This pilot study was an attempt to explore any changes in pelvic floor function following temporary SNS, and inform subsequent studies of mechanisms of action.

The status of global function of the pelvic floor is increasingly recognised as an important factor in the pathophysiology of functional bowel disorders, and dynamic imaging of the pelvic floor is increasingly acknowledged as an important assessment tool in faecal incontinence and other anorectal disorders[171, 172]. The Levator muscle receives direct nerve supply from the sacral nerves proximal to the sacral plexus[111] and is a potential target of SNS neuromodulatory process as highlighted. Nevertheless, there is very little emphasis thus far on examining global pelvic floor function following SNS.

Proctography has significantly evolved since it was first described by Burhenne in 1964[173]. As pelvic floor weakness is usually generalised, various pelvic floor compartments are best imaged simultaneously[174]. Conventionally, this has been achieved by performing evacuation proctography modified by the additional opacification of the bladder and small bowel[175-177]. However, the development of techniques of rapid image acquisition allowed pelvic floor motion to be visualised in real time using MRI which additionally defines the anatomy of pelvic organs and muscular structures in a non-invasive way that does not involve ionizing radiation.

I aimed in this study to examine changes in pelvic floor function in patients undergoing temporary SNS for faecal incontinence, utilising MR proctography in an attempt to further establish the effect of SNS on pelvic floor global function.

10.3 Methods

10.3.1 Patients and clinical assessment

A subgroup of the main study cohort was recruited to the study. Anal manometry, rectal sensory thresholds to balloon distension and electric stimulation as well as MR proctography were studied before and on the last day of temporary stimulation phase.

10.3.2 Physiological tests

Please refer to Chapter 5 for detailed description of methods of anal manometry, measurements of rectal sensory thresholds to balloon distension and to electric stimulation.

10.3.3 MR Proctography and image interpretation

MR proctography was performed using a standard superconducting MR imaging system as described in detail in Chapter 5.

The baseline proctography was performed as part of the routine pre-operative work up. The follow up imaging was performed on the last day of the phase of temporary stimulation shortly after the removal of the temporary SNS wire. The time from removal of the SNS wire and commencement of the proctogram was recorded.

All MR images were analysed by a single senior gastrointestinal radiologist who was blinded to the status of the scan and clinical data. Analyses were performed using a standard PACS workstation (Agfa Healthcare).

MR images and cine loops were analysed for a)anorectal angle (ARA) at rest; b) change in ARA with straining; c) degree of perineal descent; d) features of structural changes including rectal intussusception, rectocele and enterocele. Additionally structured assessments of rate and quality of rectal emptying were conducted.

Anorectal angle was defined as the angle between the longitudinal axis of the anal canal and the posterior rectal wall[178]. It was measured both at rest (ARA r) and at maximal strain (ARA s). The percentage of change (ARA r – ARA s/ARA r) was calculated.

The Anorectal junction was defined as the junction of the rectal ampulla and anal canal. As in previous studies, the pubococcygeal line (PCL) was considered as the line joining the inferior border of the symphysis pubis to the last coccygeal joint on a midline sagittal image[178, 179]. The positions of the bladder base, vaginal vault and anorectal junction were measured at 90° angle to the PCL which was used as the reference line*(Figure 9.1)*. These measured distances at the end of defecation were used to determine the state of descent of the three pelvic compartments[151]. Cystocele (anterior compartment descent) was defined as descent of the bladder base below the PCL. Vaginal vault descent below the PCL represented a middle compartment abnormality. Similarly, rectal descent (posterior compartment descent) was defined as descent of the anorectal junction below

the PCL. Enterocele was defined as the descent of the peritoneum containing small bowel below the PCL[151].

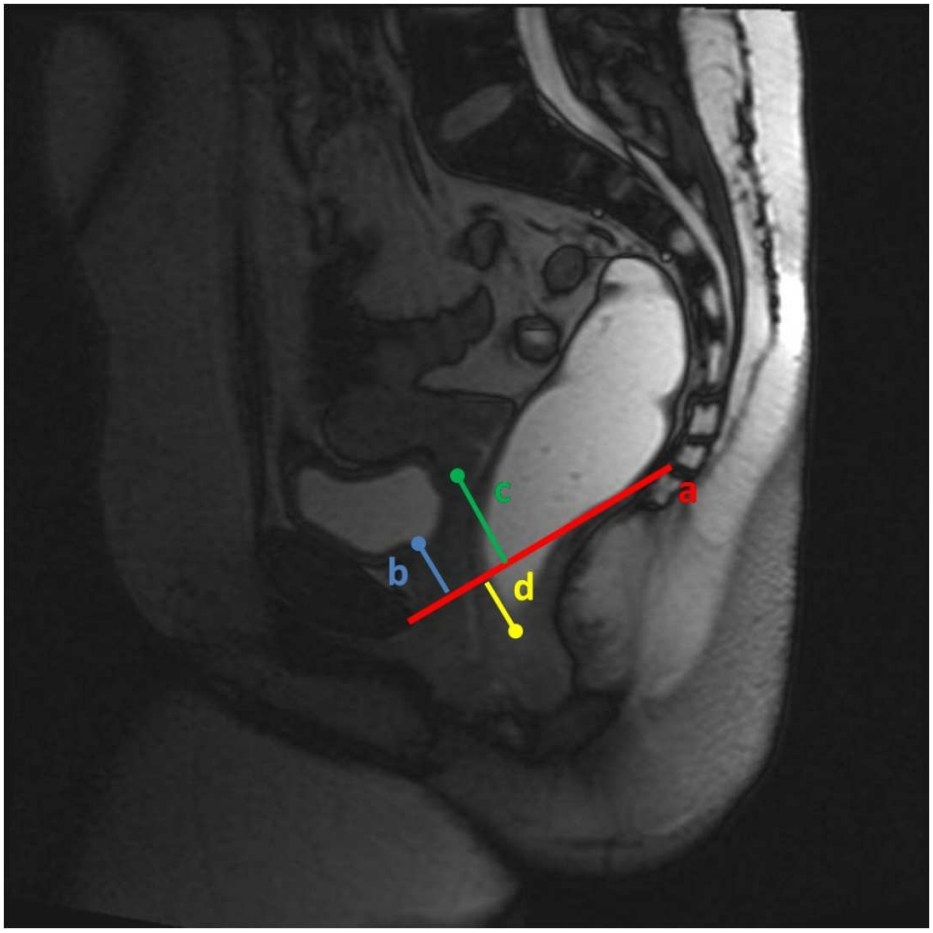


Figure 10.1 – Pubococcygeal line (a) as the reference line for descent measurements. Lines (b), (c) and (d) demonstrate measuring the amount of descent of the bladder, vagina and anorectal junction respectively.

Rectocele was defined as a protrusion of the rectal wall anterior to a line extending cranially through the anal canal. The extent of protrusion beyond this line determined the size of the rectocele. A three-grade scoring system published by other

investigators[151, 180]was used to grade the extent of any cystocele, vaginal vault descent, enterocele or rectocele *(Table 10.1)*.

Table10.1 – Grading system for MR proctography findings: §

Abnormality	Small	Moderate	Large
Cystocele	<3cm	3-6cm	>6cm
Vaginal vault descent	<3cm	3-6cm	>6cm
Enterocele	<3cm	3-6cm	>6cm
Rectal descent	<3cm	3-6cm	>6cm
Rectocele	<2cm	2-4cm	>4cm

§ Reference: Roos et al 2002[180]

Assessment of rectal evacuation was conducted using a number of parameters. Timings assigned to each individual image in the TrueFISP cone loop facilitated temporal measurements. The time to achieve maximal or full contrast evacuation was recorded. In addition, the percentage of contrast evacuated after 30 seconds of straining was measured. This was derived by calculating the ratio of the surface area of the mid rectal lumen below the first rectal fold (measured using electronic callipers in the PACS workstation) at the start of imaging, to the surface area below the same anatomical landmark at 30 seconds from the commencement of imaging. Finally, a global subjective grading of evacuation as either: Normal, Delayed, Severely Delayed or Absent was made based on the experience of the radiologist.

10.3.4 Statistical analysis

Statistical analysis was performed using *PASW® Statistics 18* software package, SPSS Inc, Chicago, Illinois, USA. Data was presented as either mean and standard deviation or median and range depending on distribution. Parameters of rectal evacuation before and after SNS were compared using Wilcoxon signed-rank test. Proportions (pelvic organ descent and grades of rectal evacuation before and after SNS) were compared using Fisher Exact test.

10.4 Results

Eight patients (7 female) undergoing temporary SNS for intractable FI were studied.

10.4.1 Patients and clinical results

The median age of patients was 57 (range, 25-77). The aetiology of FI included obstetric causes (4), idiopathic incontinence (1), post-anorectal surgery (1), scleroderma (1) and neurological (1). All patients had symptoms of incontinence significantly impacting on their lifestyle, with their mean weekly episode of incontinence at 5 ±2. Symptoms in all patients were predominantly those of urge incontinence. The mean Wexner score was 15 ±4.

Endoanal ultrasound assessment showed intact sphincters in 4 patients (50%), sphincter defects in 2 (25%) and atrophic sphincters in 2 (25%). Sphincter repair had been previously performed in 2 of the patients (evidence of residual internal sphincter defect in 1). One patient with a sphincter defect identified at the time of presentation did not undergo a repair procedure prior to SNS.

The mean duration of temporary stimulation in this cohort of patients was 20 ±3.5 days. Five patients (62.5%) had a significant positive response to the stimulation; their weekly episodes of incontinence reduced from the mean of 3 ±2 to 1 ±1 (P=0.007). Their Wexner scores also significantly dropped from the mean of 15 ±2 to 8 ±5 (P=0.004). Three patients had no significant change in symptoms during stimulation.

10.4.3 Results of MR imaging

The average interval between the removal of the temporary SNS wire and obtaining of the follow up MR proctogram was 18.4 (±5.4) minutes.

10.4.3.1 Ano-Rectal Angle (ARA)

Anorectal angle increased with straining. The degree of this increase in ARA with straining did not significantly change before and after the period of temporary SNS in this cohort of patients *(Table 10.2)*.

Table 10.2– Results of changes in ARA:

	Baseline n=8	Post-SNS n=8	P Value
ARA at rest (ARAr)	122 (108-148) 124.8 (±15)	122.5 (103-140) 122.6 (±14)	0.640 † 0.604 ‡
ARA at strain (ARAs)	141.5 (116-156) 140.75 (±12.4)	139.5 (119-148) 138.4 (±9.7)	0.547 † 0.515 ‡
ARAs minus ARAr	11.5 (0-41) 16 (±13)	15.5 (-5 to 38) 15.7 (±17.3)	1 † 0.941 ‡
Proportion of change (ARAs – ARAr/ARAr)	9% (0-37.6)	17% (0-37)	0.578 †

† Wilcoxon signed ranks
‡ Paired *t* test

10.4.3.2 Degree of pelvic organ descent

There were no cases of cystocele or significant bladder descent at rest. However 5 patients developed cystocele (3 small and 2 moderate) on straining. This was consistent after temporary SNS *(Table 10.3)*. Descent of the vaginal vault occurred with straining in three patients pre-SNS and in one patient after stimulation (p=0.559, Fisher's Exact test).The anorectal junction was found to be always below the level of the Pubo-Coccygeal Line. The rate of its descent both at rest and at strain did not significantly change after temporary SNS. Mean distances of the different pelvic organs from the PCL are demonstrated in *Table 10.4.*

10.4.3.3 Anatomical abnormalities (Enterocele, Rectocele and Intussusception)

Enterocele (small) was found in two patients pre-operatively but only in one post-SNS ($p>0.999$). Five Rectoceles (1 small and 4 moderate) were found pre- and post- SNS. Two patients had internal rectal intussusceptions pre-operatively but only one was found post-SNS.

Table 10.3– Structural abnormalities detected on MR proctography:

	Before SNS			After Temporary SNS			P value†
	Small	Moderate	Large	Small	Moderate	Large	
Bladder descent (cystocele):							
at rest	0/8	0/8	0/8	0/8	0/8	0/8	-
at strain	3/8	2/8	0/8	3/8	2/8	0/8	-
Vaginal vault descent:§							
at rest	0/7	0/7	0/7	0/7	0/7	0/7	-
at strain	3/7	0/7	0/7	1/7	0/7	0/7	0.559
Enterocele	2/8	0/8	0/8	1/8	0/8	0/8	1
Rectocele	1/8	4/8	0/8	1/8	4/8	0/8	-

† Fisher's Exact test
§ total case number is 7 as one patient is male

Table 10.4 – Distances of different pelvic organs from the PCL:

	Before SNS n=8	Post SNS n=8	P value †
Bladder distance at rest at strain	 2.1 (±1.7) -0.7 (±3)	 2.2 (±1.6) -0.4 (±3)	 0.585 0.08
Vaginal distance at rest at strain	 3.7 (±1.2) 0 (±1.5)	 3.7 (±1) 0.5 (±1.4)	 0.968 0.299
Anorectal junction distance at rest at strain	 -2.5 (±1) -5.4 (±2.5)	 -3.1 (±1.7) -5.3 (±2.3)	 0.282 0.719

† Paired *t* test

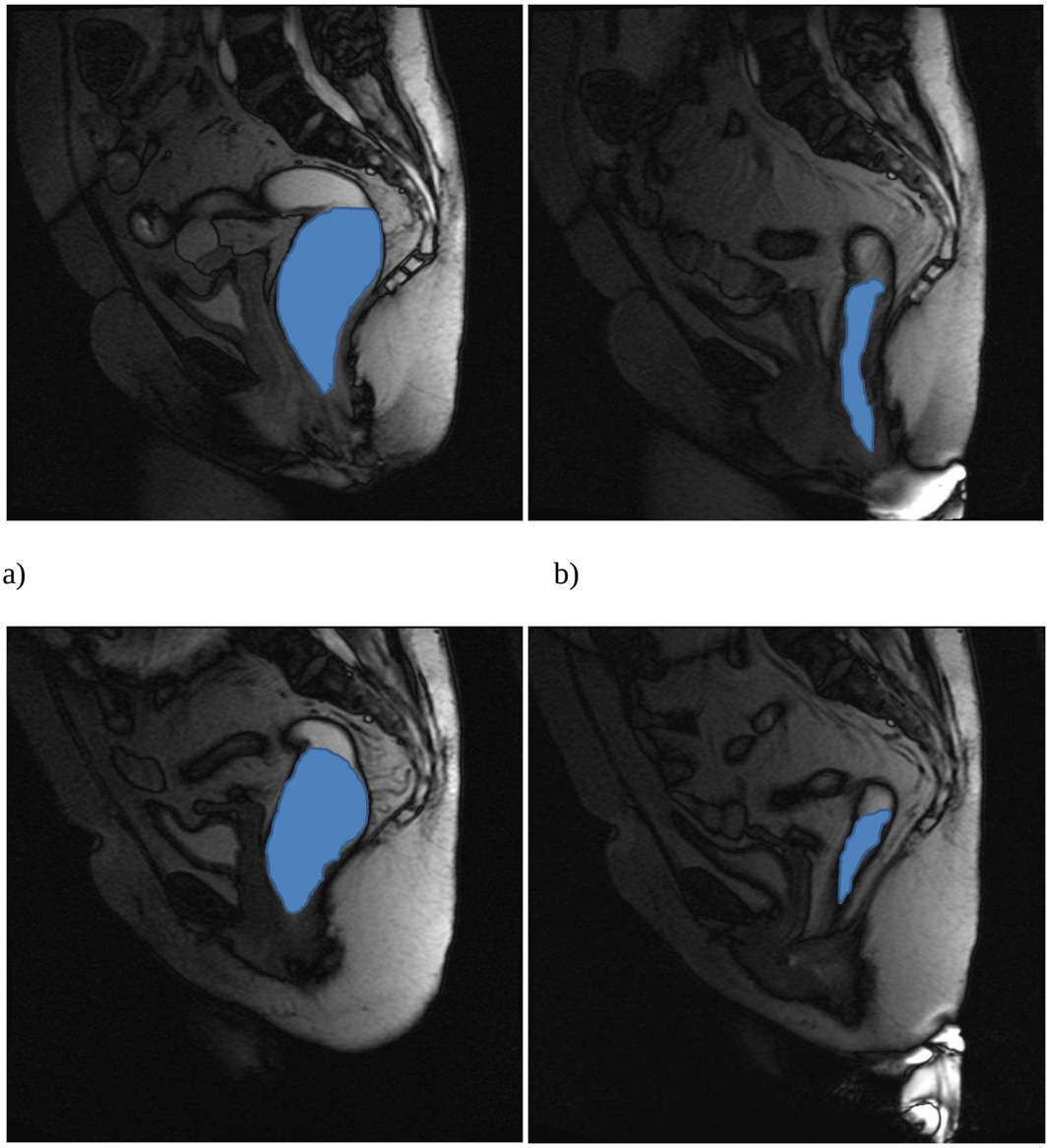
10.4.3.4 Rectal evacuation

The time taken to maximal evacuation was reduced with temporary SNS with a statistical result trending for significance (27 seconds versus 16 seconds, P=0.068). This was also associated with significant increase in the proportion of contrast Gel evacuated at the end of 30 seconds from attempting rectal evacuation (baseline: 40.2%, post-SNS: 70%; P=0.046). The overall subjective grading of the evacuation process did not significantly change when assessed after stimulation; nevertheless, reduction in the number of those who were graded as 'Severely Delayed' was noted *(Table 10.5)*. Figure 10.2 and 10.3 show MR images from two cases demonstrating the technique of analysis.

Table 10.5– MR proctography evacuation parameters in the whole cohort:

	Baseline n=8	Post-SNS n=8	P value
Time to maximal evacuation (seconds)§	27 (16-123)	16 (8-69)	0.068 †
Percentage of evacuated Gel at 30sec (%)	24.9 (0-88)	49.1 (0-100)	0.031 †
Grading of rectal emptying: Normal Delayed Severely Delayed Absent	 3 (37.5%) 1 (12.5%) 2 (25%) 2 (25%)	 4 (50%) 1 (12.5%) 1 (12.5%) 2 (25%)	 >0.999 ‡

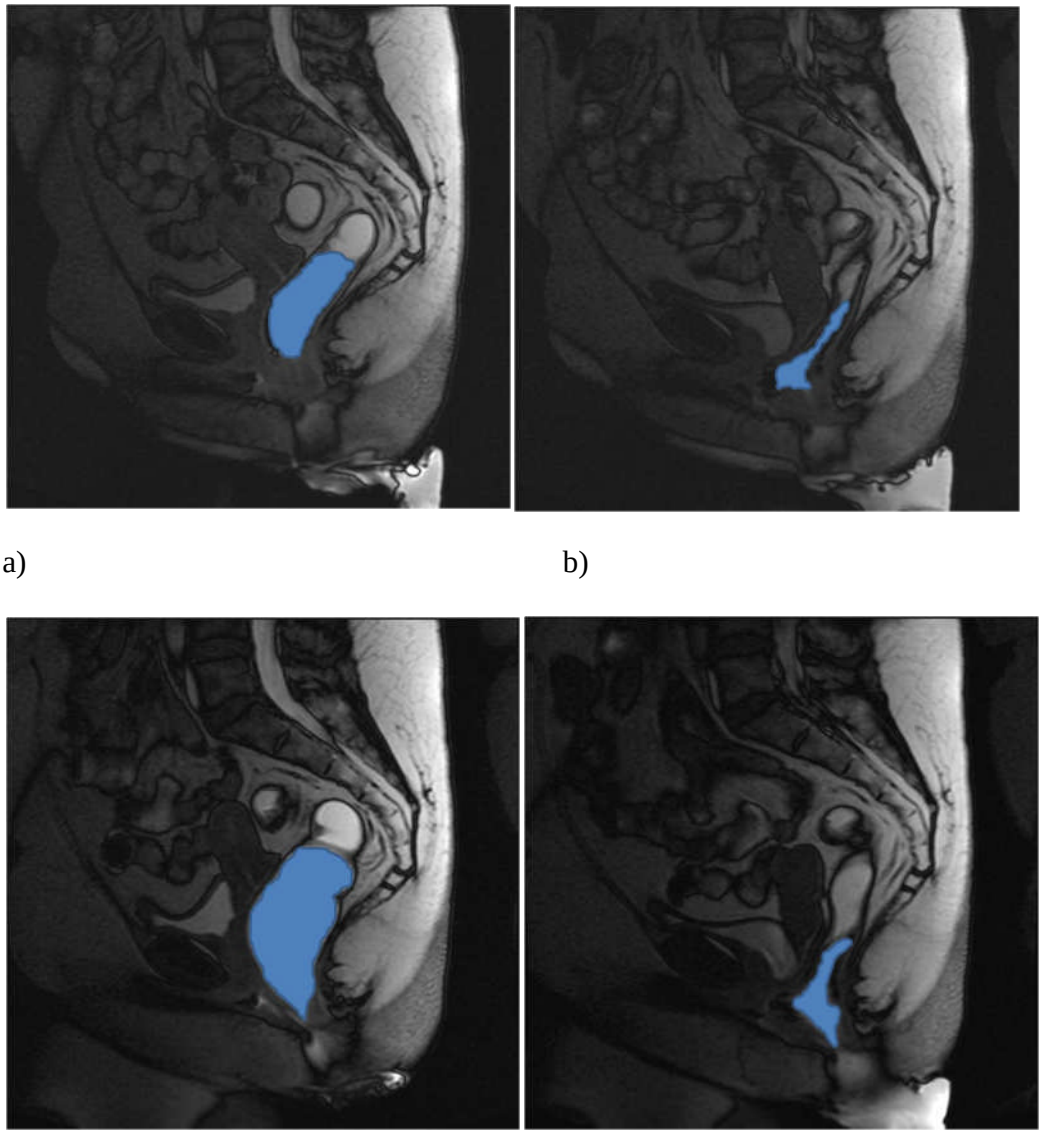
† Wilcoxon Signed Ranks
‡ Fisher Exact test
§ one patient was excluded as follow up scan was performed on two settings



a) b)

c) d)

Figure 10.2 – MR images showing the shadow of contrast below the first mucosal fold at the beginning and end of evacuation (before SNS: a and b; and after SNS: c and d)



a) b)

c) d)

Figure 10.3 – MR images showing the shadow of contrast below the first mucosal fold at the beginning and end of evacuation (before SNS: a and b; and after SNS: c and d)

10.5 Discussion

10.5.1 Principal findings

This prospective study examined the changes demonstrated on MR proctography following temporary SNS in a cohort of patients who were treated for intractable faecal incontinence.

Repeat MR imaging following SNS suggests improved rectal emptying at the end of the phase of temporary stimulation. The time to achieve maximal evacuation and the amount of evacuated contrast gel in the first 30 seconds was found to be significantly better in the post-SNS scans.

This approach to studying rectal evacuation on MR proctography is relatively novel; however, the above mentioned markers were considered surrogate indicators of the quality and coordination of rectal evacuation in real-life.

The study also revealed that this improvement in characteristics of rectal emptying are not associated with structural changes in the pelvic floor; the rate of pelvic organ descent, presence of rectoceles or other structural abnormalities did not change on repeat imaging after temporary stimulation. This suggests that the potential improvement associated in rectal emptying with SNS is a neurologically mediated change to the physiological process of evacuation rather than a result of structural pelvic floor change.

10.5.2 Strengths of the study

As far as I know, this is the first study to utilise MR proctography in order to examine potential mechanisms of SNS. Evacuation proctography is an evolving technique to assess pelvic floor abnormalities and is increasingly routinely used to assess patients with faecal incontinence[171]. The use of MR proctography is superseding alternative methods of proctography as it non-invasively delineates the anatomy of pelvic floor muscles and pelvic organs without using ionising radiation [150, 178]. Although, proctography is not an exact simulation of defecation as the physical properties of the contrast and its method of delivery into the rectum significantly differ from normal stools, it does provide a simple and reproducible study for the evaluation of defaecatory disorders if certain parameters are standardized [181].

The main purposes of proctography are to provide images of rectal configuration throughout the phases of evacuation and also to provide an assessment of whether voiding is normal or prolonged[182]. The assessment of completeness of evacuation and its rate are considered an essential part of the examination [183] and therefore, it is considered a functional test. Some authors, however, feel that because the findings are based on voluntary rectal evacuation of a paste and not physiologic defecation of stools which is accompanied by colonic contraction and complex coordination of reflexes it should not be considered as a test of function. Some for instance suggest modifying the technique by instilling contrast until an urge to evacuate is elicited to render the test more physiological.

I feel however, that the test's methodology should be standardized (including the same amount of contrast) so that a meaningful comparison of the rate and completeness of rectal evacuation can be made with established values derived from normal subjects [184]. However, the crucial point remains that this is not a functional test of physiologic defecation; it is rather a functional test of the process of rectal evacuation in a standardized simulated fashion; terminology is crucial.

Because of technical reasons related to the presence of the wire and the electric stimulator, the follow up MR imaging could not be performed whilst patients were still undergoing stimulation. Nevertheless, the interval between the removal of the stimulation wire and the scanning in this cohort of patients was significantly short. This means that the follow up imaging does reflect the status with ongoing SNS stimulation, which is believed to have some carry-on effect for at least few days after cessation of stimulation.

10.5.3 Weaknesses of the study

Nevertheless, one of the limitations of this study is that the MR protocols used did not include dynamic imaging of the pelvic floor during squeeze. This means that full assessment of potential changes in the puborectalis function cannot be derived from this study. Some authors have suggested that puborectalis dysfunction can be demonstrated if only minimal changes in the anorectal angle are demonstrated on dynamic imaging at rest, straining and squeezing [171, 185]. However, other authors have failed to demonstrate

differences in ARA at various states between asymptomatic volunteers and patients with FI or constipation [186].

Additionally, the MR proctogram in this study was performed in the supine position and not in an open configuration MRI system as this was not available at our centre. This is not ideal and might have an impact on conclusions drawn about rectal evacuation which clearly is not physiological in the supine position. Several investigators have examined the potential impact of performing this dynamic examination in the supine position, mostly revealing that variations in pelvic floor descent and organ prolapsed are similarly observed at supine MR compared to upright MR or fluoroscopy [150, 151, 187]. Additionally, the technique was standardised at both pre- and post- stimulation imaging and an improvement in rectal evacuation on the repeat imaging secondary to less associated embarrassment during second setting is unlikely.

Another potential limitation of this study is the small number of recruited subjects and the possibility of selection bias as the study centre is a tertiary referral unit. Nevertheless, this is a mechanistic study which only aims at interpreting findings of control-subject imaging. More studies are no doubt required to further establish the accuracy and reproducibility of these findings. Patients were recruited to the study prospectively and they represent a cohort of consecutive consenting patients.

10.5.4 Comparison of study data with other studies in the literature

Only few studies have examined rectal evacuation with SNS. Studies of SNS in constipation predominantly examined symptom change and transit times rather than physiological changes with evacuation [88, 89, 188]. Hirabayashi et al conducted an experimental study in dogs and demonstrated that sacral nerve stimulation led to the occurrence of motility patterns similar to those demonstrated during spontaneous defecation, namely the development of giant migrating contractions of the distal colon propagating to the rectum with an associated relaxation response in the rectum and the internal anal sphincter [135]. Similar findings were also reported by Bhadra et al[136]. The intestinal migrating motor complexes are programmed by the enteric nervous system which is under control of the Central Nervous System via efferent and afferent sympathetic, sensory and parasympathetic systems. Langley and Anderson[9] have demonstrated that the parasympathetic control of the left colon is distributed through the Sacral parasympathetic plexus; it is likely that this is the culprit of influence mediated by SNS. We cannot comment about the patterns of colonic migrating complexes in our cohort of patients as MR proctography does not reveal this information; but nevertheless it accurately demonstrates the anorectal component of the process.

Most studies which looked at effects of SNS on rectal functions examined sensory function or compliance; often revealing inconsistent findings about changes in rectal sensory thresholds with the stimulation[79, 91, 97, 98, 120]. In Study 1, I demonstrated that rectal wall pressures associated with Urgency and Maximal Tolerated thresholds were

significantly higher after SNS. However, in the cohort of patients in this study there were no significant anorectal sensory changes after stimulation. This could suggest that changes in evacuation in this group of patients are not mediated via enhancement of rectal sensory function; however, the lack of demonstrated sensory change is most likely due to the small number of subjects.

The potential improvement in rectal evacuation with SNS is likely to be a result of neuromodulation enhancing evacuation reflexes and influencing the sacral autonomic centre; however, a combination of a number of mechanisms and pathways including sensory mediated changes could be in play; as the process of bowel evacuation is clearly an orchestration between the somatic and the autonomic nervous systems. Direct effect on the pelvic floor musculature resulting in improved relaxation is also a possibility, although changes in ARA were not demonstrated in this study.

10.5.5 Clinical implications

Improved rectal evacuation as a potential underlying mechanism of SNS in faecally incontinent patients is a plausible proposition. The findings of this study suggest that more attention should be paid to objective symptomatic assessment of evacuation patterns in patients undergoing SNS for faecal incontinence. Moreover, thorough assessment of these patients should probably include the routine use of MR proctography.

10.5.6 Suggestions for future research

Larger studies are required to further establish the reproducibility of the techniques and findings of this research. On another level, further studies of the sacral parasympathetic centre of evacuation and the contractility activity induced by its stimulation are required. The introduction of high resolution manometry techniques and advanced ambulatory methods should enable detailed studies of these changes in patients and asymptomatic control subjects.

Chapter 11

Summary and Conclusions

11.1 My work is mainly concerned with potential SNS mechanisms, through studying the anorecal physiological and structural changes associated with stimulation. Clinical results are also discussed but they do not represent the focus of the work. Assessment of clinical response was based on the standard commonly used tools and physiological findings were analysed for the subgroups of responders and nonresponders. It is to be noted here, that the focus of the study was effects of temporary SNS, and it is not clear whether the findings can be extrapolated to effects associated with permanent SNS or not.

11.2 The potential target organs of SNS in faecal incontinence are the following:

a) sphincter and pelvic floor muscles (somatic and autonomic innervation)

b) the sensorimotor function of the rectum (autonomic innervation)

11.3 Increased sphincter pressures (especially or exclusively the squeeze pressure) is almost the only consistent finding of studies examining potential physiological mechanisms of SNS.

11.3.1 Hypothetically speaking, this increase in sphincter pressures with SNS could be the result of either:

a) continuous low threshold stimulation of efferent nerves which supply the sphincter/pelvic floor muscles leading to direct improvement of muscle function, with or without muscular changes (change of fast twitch fibres to slow twitch fatigue resistant fibres).

b) stimulation of afferents or autonomic nerves leading to improved sphincter function through a reflex mechanism or the process known as neuromodulation.

11.3.2 The only direct evidence on neuromodulation as the underlying mechanism for the improvement in sphincter function is from a single landmark study using EMG and measuring the interval from acute stimulation of S3 to sphincter contraction (this was found to be significantly longer than would be expected if the contraction was a result of efferent stimulation)[113].

11.3.3 There is however indirect evidence of neuromodulation. This is in the form of findings of other changes in anorecal functions with SNS suggesting that stimulation of afferent or autonomic nerves does exist.

11.3.4 I think that EMG studies of latency of sphincter contraction with acute S3 stimulation ought to be repeated in a larger number of cases to further establish whether indeed the contraction of the EAS is secondary to reflexly mediated pathways or a result of direct efferent stimulation as this is a crucial piece of evidence in the whole matter. Utilizing other newly developed investigative technologies such as functional MRI to examine this very issue can also be considered.

11.3.5 With regard to sphincter pressures, I attempted to answer the following questions:

a) does sphincter pressure change after a period of SNS? (to further validate the findings reported in the literature)

b) does the acute alteration of the device status (On/Off) changes anal pressures?: the answer to this question was thought to be a way of addressing whether the increase in sphincter pressures is due to efferent stimulation or a more complex mechanism; with the premise that if it is due to efferent stimulation, switching it Off will lead to a sudden drop in the pressures and switching it On will lead to an increase.

11.4 Another way of attempting to understand the underlying mechanism behind the observed increase in sphincter pressures (direct or neuromodulatory) is to establish whether SNS causes changes in other target organ functions. For instance, if it is established that SNS causes changes to autonomic-mediated anorectal functions, it might be concluded that the increase in sphincter pressures associated with it is a result of more complex pathways than just direct efferent stimulation.

11.4.1 In that regard, I have attempted to examine the potential changes associated with SNS in the following aspects:

a) the sensorimotor function of the rectum (rectal thresholds and rectal compliance) –*both an intrinsic and an extrinsic autonomic function*

b) the reflex function of the rectum (RAIR) – *a locally mediated reflex*

c) any structural changes to the pelvic floor or any changes to its global function (marker being rectal evacuation) – *a combination of somatic and autonomic function*

11.5 On anal pressures:

11.5.1 I found that squeeze sphincter pressures do increase with SNS stimulation (in both responders and non-responders) but On/Off alteration (performed at the end of temporary stimulation phase) doesn't effect a change.

11.5.2 I found that the resting pressure have increased in responders only.

11.6 On rectal sensorimotor function:

11.6.1 Rectal compliance is influenced by two factors: a) rectal sensory thresholds; and b) rectal wall contractility and is therefore an autonomic function.

11.6.2 In my study, I found that rectal compliance didn't significantly change with SNS either in responders or non-responders

11.6.3 However, studying rectal sensory thresholds revealed that the rectal pressures associated with Urge and Maximally Tolerated Volumes were increased with SNS. The actual volumes associated with these thresholds didn't significantly change. These

findings were predominantly observed in Responders. This argues for an afferent-mediated (autonomic) mechanism.

11.6.4 It is difficult to interpret and explain the above mentioned observation as it is suggesting that that the pressure is changing without the change in volume. This could be suggestive of changes occurring to rectal tone or contractility.

11.6.5 The findings however are suggestive of an autonomic-mediated change.

11.7 On RAIR:

11.7.1 The RAIR is thought to be a locally mediated reflex involving the intrinsic enteric nervous system. (increased pressure within the rectum leads to reflex relaxation of internal sphincter allowing sampling of the contents delivered to the rectum by the specialized proximal anal mucosa). Studying RAIR changes is of particular relevance in the context of understanding SNS, as it represents a physiological phenomenon where the two separate paradigms of sphincteric and suprasphincteric factors can be jointly examined.

11.7.2 The components of the reflex are: the latency period, the amplitude and the recovery time. The latency period reflects duration of neurological synaptic transmission. The amplitude reflects the muscular component. The recovery period reflects partly the neurological factors and partly the muscle tone.

11.7.3 Interestingly, I have found that the RAIR recovery time is shortened after temporary SNS. Other components of the reflex didn't change with SNS. This can be explained by influence of SNS on neuronal transmission within the intrinsic enteric nervous system. However, it can also be explained by changes to the internal anal sphincter tone mediated by increased sympathetic discharge or decreased parasympathetic discharge. This will require further studies potentially using pharmacological antagonists.

11.7.4 The change noted in the RAIR recovery time after SNS suggests that SNS has mechanisms other than mere efferent somatic stimulation. It suggests that SNS does influence the intrinsic enteric nervous pathways. Also, it is another evidence of potential effect on the autonomic anorectal innervation.

11.8 On MR proctography results:

11.8.1 MR proctography is a test of structure and there is controversy as to whether it can be used to assess function of pelvic floor function. However, it does represent a reasonably good evaluation of rectal emptying considering the artificiality of the test and the fact that it is performed in the supine position.

11.8.2 Rectal evacuation represents an autonomic spinal reflex which is moderated by central influence. It represents a marker of combined sensory and motor function of the rectum.

11.8.3 My study using MR proctography revealed that:

a) the duration of emptying is slightly reduced when assessed after SNS (not statistically significant).

b) the amount of emptied contrast at 30sec from the onset of evacuation is significantly larger when assessed after SNS.

These measures are not necessarily direct indication of status of rectal evacuation; however, they are significant surrogate markers.

11.8.4 The explanation of improved rectal emptying with SNS is most likely multi-factorial:

a) SNS was found to have altered the rectal pressures associated with distension sensory thresholds and therefore it is possible that it improves the receptiveness of the rectum to the faecal load.

b)SNS was found to have influenced the RAIR parameters and therefore it is likely that SNS is influencing the intrinsic anorectal reflexes which are bound to be involved in the process of the defecation reflex.

11.8.5 It is to be noted in this context that some clinical studies have already demonstrated positive results in patients with constipation (both slow transit and evacuatory difficulty) treated with SNS.

11.9 On possible placebo effect:

11.9.1 The possibility of a placebo effect was examined by two randomized controlled cross-over trials reported in the literature. Overall results suggested that the clinical effect is associated with the ON status of the stimulation; however, in a number of patients either positive clinical effects were reported during the OFF period or patients were unable to determine which period (device ON or device OFF) was more preferable to them.

11.9.2 I feel that there are two aspects which are related to the discussion regarding a possible placebo effect:

a) the inability to demonstrate a definite consistent physiological marker of response or a consistent physiological change with stimulation makes it possible still to consider a placebo effect.

b) the complex psychological profile of patients suffering with functional anorectal symptoms does probably have a bearing on understanding their response to intervention. Their psychological profile could be either the precipitating factor of their persistent symptoms or the result of their dysfunctional disease. However, it must have a bearing on their ultimate response to treatment and very little work has been done in this field.

11.9.3 With regard to point 9.2a the following ought to be mentioned:

a) the current anorectal physiological diagnostics are probably not sufficiently sensitive to pick up the degree of complexity of the physiology of the anorectum and the changes that functionally occur

b) the range of normality of the physiological parameters recorded is so large that it is difficult to interpret findings unless there is a very large number of patients being studied

c) the physiological parameters measured often do not reflect the clinical state of the patient; i.e. the association between physiological results and clinical condition of the patient is not always consistent. This usually makes the interpretation of physiological findings rather difficult.

11.10 Limitations

11.10.1 The studies' limitations have been discussed in detail for each study separately. The main limitation of the whole project is the small number of subjects.

11.10.2 A significant limitation of this project is that it was of an evolving design. Not all subjects were included in all studies according to their stage of recruitment and the evolution of thought and study process.

11.10.3 Subsequent to the point 11.10.1, another design limitation is that the surgical technique (namely the type of anaesthesia under which the surgery was

performed) varied between the patients as the more temporary SNS cases were performed under local anaesthesia with the evolution and development of the surgical expertise in the technique.

11.11 Summary and future directions:

11.11.1 In summary, I can conclude that the various experiments conducted in this project have demonstrated significant evidence of influence on the anorectal autonomic innervation by SNS.

11.11.2 The most persistent physiological finding with SNS remains to be the increase in anal squeeze pressures. This is likely in view of the evidence explained above to be a result of afferent mediated complex mechanism rather than mere direct efferent somatic stimulation.

11.11.3 Future research remains urgently required. Understanding of the underlying mechanisms of action will be desirable as it will better inform the process of patient selection. Furthermore, a physiological marker of response could potentially be recognized and used as a selector for responders.

11.11.4 I feel that further research on the latency of sphincter contraction using EMG following acute S3 stimulation is required. The study of Fowler et al had a small

number of patients and such research is going to be crucial in establishing whether effects are direct or afferent-mediated.

11.11.5 The site of action/neuromodulation initiated by SNS is not yet established. Some of the results in this project suggest it could be the intrinsic enteric pathways. However, I also demonstrate that it has influence on the autonomic function and squeeze pressures and therefore this site might be primarily the peripheral nerve (autonomic and somatic) and the spinal cord centers.

11.11.6 Furthermore, some authors have demonstrated changes occurring at cortical levels. This potential alteration and afferent interaction with the Cortex has not been studied in this project. Work on changes involving the cortical evoked potentials during SNS is warranted.

11.11.7 Mechanisms of SNS effects in faecal incontinence are no doubt complex. This is a reflection of the complexity of the innervation to the anorectum (and the whole gut) and its interaction with the central nervous system (the gut-brain axis).

11.11.8 I propose the study of rectal compliance and other anorectal physiological parameters with and without SNS whilst the patient is under general anaesthetic (during the episode of insertion of the temporary stimulation wire). This will be a way of assessing the anorectal physiological parameters in isolation of the conscious influence of the central nervous system. Furthermore, it will allow us to study the anorectal

physiological changes sustained at various amplitudes of stimulation; some of which cannot be tolerated during the wake status. Different nerve fibres within a mixed nerve have significantly different thresholds to electric stimulation.

11.11.9 I propose studying anorectal physiological parameters before and after SNS using the high resolution manometry techniques.

11.11.10 I suggest comparative examination of the physiological changes associated with other forms of induction of neuromodulation (namely PTNS, Pudendal nerve stimulation and Transcutaneous SNS).

11.11.11 Further work examining the psychological profile of patients undergoing SNS and establishing if there is any difference between responders and non-responders. Future studies at the unit will look at questionnaire assessment of these factors in relation to the findings identified in this work.

11.11.12 Studies with longer follow up and long term results are required.

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Appendices

Appendix 1: Study 1 data (Chapter 7)

Study 1: Patients and clinical results

Pt ID	Sex	Age	Aetiology	EAUS	Duration of stim. (days)	Baseline Wexner	FU Wexner	Baseline FI episodes/wk	FU FI episodes/wk	Responder
2	f	37	Neuro (SAH)	Intact	22	17	1	4	0	Yes
3	f	56	Obstetric	Intact	16	7	10	8	7	Yes
5	f	48	Obstetric	Intact	22	16	4	4	1.5	Yes
6	f	39	Rect Prolapse	Atrophy	15	15	15	5	4	No
7	f	49	Post STARR	Intact	22	10	8	4	1	Yes
8	f	61	Obstetric	Defect	20	18	3	4	0	Yes
9	f	53	Pelvic surg	Intact	10	12	4	4.5	0.5	Yes
10	f	42	Idiopathic	Intact	21	14	3	1	0	Yes
11	f	72	Obstetric	Intact	21	16	12	2	1.5	Yes
12	f	30	Obstetric	Defect	15	14	10	4	2	No
14	f	63	Obstetric	Defect	21	14	8	5	1	Yes
15	f	74	Obstetric	Intact	21	13	13	3.5	4	No
17	f	50	Idiopathic	Intact	8	15	15	7	2	No
19	f	52	Idiopathic	Intact	21	12	6	1	0	No
20	f	47	Obstetric	Defect	12	15	11	4	3.5	Yes
21	f	70	Atrophy	Atrophy	21	14	6	7	0	Yes
22	f	46	Scleroderma	Atrophy	21	19	17	5	2	Yes
23	f	38	Idiopathic	Intact	21	14	16	7	4.5	No
24	f	48	Obstetric	Defect	21	11	0	7	0	Yes
28	f	48	Obstetric	Intact	21	13	4	5	2	Yes
29	m	77	Idiopathic	Atrophy	21	9	14	7	1.5	No
30	f	49	Obstetric	Defect	21	13	5	3	1	Yes
3P	f	43	Obstetric	Intact	23	16	8	6	1.5	Yes

Study 1: Anal manometry and rectal compliance data:

Pt ID	Responder	Baseline resting	FU resting	Baseline squeeze	FU squeeze	Baseline compliance	Post-SNS compliance	Δ compliance
2	Yes	59	77	156	243	10.31	6.21	-4.1
3	Yes	16	54	30	189	19.06	13.33	-5.73
5	Yes	28	60	119	77	11.45	7.26	-4.19
6	No	21	16	6	16	21.77	11.51	-10.26
7	Yes	39	97	14	86	15.15	12.38	-2.77
8	Yes	40	22	40	54	8.4	11.37	+2.97
9	Yes	54	46	38	64	10	21.98	+11.98
10	Yes	63	41	129	123	7.94	7.53	-0.41
11	Yes	27	45	53	54	18.93	17.25	-1.68
12	No	18	24	27	38	9.37	7.7	-1.67
14	Yes	23	26	119	171	15.05	15.46	+0.41
15	No	38	21	30	46	15.13	14.89	-0.24
17	No	58	52	31	46	11.04	8.76	-2.28
19	No	113	115	142	156	11.18	12.77	+1.59
20	Yes	60	57	28	25	12.62	11.6	-1.02
21	Yes	44	43	89	89	11.99	15.56	+3.57
22	Yes	21	36	62	74	10.51	15.31	+4.8
23	No	62	119	34	54	14.83	14.23	-0.6
24	Yes	77	88	39	65	9.53	12	+2.47
28	Yes	62	74	47	54	11.5	12.38	+0.88
29	No	68	56	101	185	13.72	18.75	+5.03
30	Yes	32	64	26	40	10.37	12.92	+2.55
3P	Yes	16	28	53	80	12.83	12.34	-0.49

Study 1: Rectal sensory distension thresholds:

Pt ID	Responder	Baseline FS Vol	FU FS Vol	Baseline T Press	FU T Press	Baseline U Vol	FU U Vol	Baseline U Press	FU U Press	Baseline MTV Vol	FU MTV Vol	Baseline MTV Press	FU MTV Press
2	Yes	35	120	-	8	50	212	-	23.5	70	260	-	32.5
3	Yes	25	23	11	11	90	30	15	15.3	180	60	23	22.5
5	Yes	30	34	7	7.5	50	80	15	15	130	106	22.8	19
6	No	56	40	14.6	11.3	135	70	19.1	15	138	160	23.4	19.6
7	Yes	110	96	14.6	10.8	236	210	22.2	18.6	250	290	26.8	27.1
8	Yes	100	98	7	7.3	157	150	11	14.5	190	245	14.7	28
9	Yes	35	73	8.5	16.7	95	70	11.2	20.3	180	187	8.5	29.6
10	Yes	40	160	-	12.3	100	216	-	20.4	120	283	-	32.7
11	Yes	80	104	7	17.7	150	150	15.2	22.8	170	208	19	27.1
12	No	68	57	7.2	7.1	129	109	11.3	15	163	145	14.9	19
14	Yes	138	82	11	6.4	191	140	15.4	11.1	225	166	18.3	14.3
15	No	29	61	7.8	11	77	125	12	14.6	136	174	16.1	19.3
17	No	40	104	-	20.1	80	149	-	24.7	120	195	-	34.5
19	No	65	49	16.4	19.4	100	148	20	27	167	178	27.8	30.4
20	Yes	100	115	23.1	22.9	150	299	26.7	42.7	195	307	30.8	43.3
21	Yes	105	35	14.9	11.2	166	118	18.5	19.4	193	212	21.6	27
22	Yes	100	46	8.8	7.2	172	99	15.5	15.4	219	140	19.6	19.4
23	No	100	31	20	14.6	150	109	24.1	23.4	240	265	31.9	38.8
24	Yes	87	98	10.7	10.9	109	137	11	16.2	125	157	14.9	19.9
28	Yes	27	69	8	15.5	98	228	17.8	28.2	88	252	20.1	33.6
29	No	>400	>400	>40	>40	>400	>400	>40	>40	>400	>400	>40	>40
30	Yes	62	64	15.3	15	133	150	23.6	27.1	203	204	31.8	27.1
3P	Yes	160	82	11.4	7.8	203	150	14	11.7	271	286	27.8	29

Appendix 2: Study 2 data (Chapter 8)

Study 2: Patient demographics and clinical data

Pt ID	Group †	Sex	Age	EAUS	Stim days	Response	Baseline Wexner	FU Wexner	Baseline SF-36	FU SF-36
1	1	F	40	Intact	16	Yes	13	7	61	76
3	1	F	56	Intact	16	Yes	7	10	51	29
5	1	F	48	Intact	22	Yes	16	4	69	89
7	1	F	49	Intact	22	Yes	10	8	23	42
10	1	F	40	Intact	21	Yes	14	3	51	78
11	1	F	71	Intact	21	Yes	16	12	46	47
21	1	F	70	Atrophy	21	Yes	14	6	-	27
23	1	F	37	Intact	21	No	14	16	17	12
30	1	F	49	Defect	21	Yes	13	5	51	53
3P	1	F	42	Intact	23	Yes	16	8	25	74
2	2	F	37	Intact	22	Yes	17	1	-	-
8	2	F	61	Defect	20	Yes	18	3	82	89
19	2	F	52	Intact	21	No	12	6	27	46
24	2	F	48	Defect	21	Yes	11	0	28	-
33	2	F	60	Intact	21	Yes	14	6	-	-
34	2	F	66	Atrophy	21	Yes	16	13	48	32
35	2	F	54	Intact	21	No	19	18	29	-

† Group 1: ON then OFF; Group 2: OFF then ON

Study 2: Anal pressures:

Pt ID	Study Group	Baseline Resting	FU Resting ON	FU Resting OFF	Baseline Squeeze	FU Squeeze ON	FU Squeeze OFF
1	1	50	26	64	24	38	29
3	1	16	54	70	30	189	159
5	1	28	60	39	119	77	124
7	1	39	97	114	14	86	49
10	1	63	41	51	129	123	111
11	1	27	45	51	53	54	46
21	1	44	43	43	89	89	60
23	1	62	119	118	34	54	56
30	1	32	64	76	26	40	53
3P	1	16	28	43	53	80	60
2	2	59	77	37	156	243	270
8	2	40	22	27	40	54	50
19	2	113	115	114	142	156	174
24	2	77	88	72	39	65	62
33	2	100	69	67	38	84	98
34	2	72	38	50	134	90	138
35	2	68	81	81	40	39	39

Appendix 3: Study 3 data (Chapter 9)

Study 3: Patients and Clinical Data:

Pt ID	Sex	Age	Stim. days	Aetiology	EAUS	Baseline Wexner	FU Wexner	Responder
15	f	74	21	Obstetric	Intact	13	13	No
17	f	50	-	Idiopathic	Intact	15	15	No
20	f	47	12	Obstetric	Defect	15	11	Yes
21	f	70	21	Atrophy	Atrophy	14	6	Yes
23	f	37	21	Idiopathic	Intact	14	16	No
24	f	48	21	Obstetric	Defect	11	0	Yes
28	f	47	21	Obstetric	Intact	13	4	Yes
29	m	77	21	Idiopathic	Atrophy	9	14	No
30	f	49	21	Obstetric	Defect	13	5	Yes
31	f	49	21	Obstetric	Defect	13	3	Yes
32	f	25	11	Obstetric	Intact	20	-	No
33	f	60	21	Post STARR	Intact	14	6	Yes
35	f	54	21	Idiopathic	Intact	19	18	No
36	f	66	21	Obstetric	Defect	18	12	Yes

Study 3: Anal manometry, rectal compliance and rectal sensory thresholds:

Pt ID	Baseline Resting	FU Resting	Baseline Squeeze	FU Squeeze	Baseline rectal compliance	FU rectal compliance	Baseline FS Vol	FU FS Vol	Baseline U Vol	FU U Vol	Baseline MTV Vol	FU MTV Vol
15	38	21	30	46	15.13	14.89	29	61	77	125	136	174
17	58	52	31	46	11.04	8.76	40	104	80	149	120	195
20	60	57	28	25	12.62	-	100	-	150	-	195	-
21	44	43	89	89	11.99	15.56	105	35	166	118	193	212
23	62	119	34	54	14.83	14.23	100	31	150	109	240	265
24	77	88	39	65	9.53	12	87	98	109	137	125	157
28	62	74	47	54	11.5	12.38	27	69	98	228	88	252
29	68	56	101	185	13.72	18.75	>400	>400	>400	>400	>400	>400
30	32	64	26	40	10.37	12.92	62	64	133	150	203	204
31	81	46	33	60	10	-	73	20	110	60	175	140
32	56	70	38	22	-	-	20	-	30	-	40	-
33	100	69	38	84	15	-	52	50	76	110	95	160
35	68	81	40	39	-	-	30	50	100	90	150	110
36	62	60	29	8	-	-	20	60	40	90	105	120

Study 3: RAIR parameters: baseline vs. post-SNS:

Pt ID	Responder	Baseline latency	FU latency	Baseline recovery time	FU recovery time	Baseline total duration	FU total duration
15	No	0.4	1.4	3	1.6	8.4	7
17	No	1.4	2.2	11.2	10.3	15.6	15.5
20	Yes	0.4	0.8	8.8	4.7	13.9	8.7
21	Yes	4.3	5.4	12.5	2.9	26.8	11.3
23	No	1.8	2.8	5.6	1.7	10.3	5.6
24	Yes	1	0.4	7.8	2.6	14.3	8.7
28	Yes	0.8	1	4.6	5.8	10.6	11.4
29	No	1.6	1.2	13.7	5.3	24.8	10.4
30	Yes	2.4	1.1	8.4	5.7	13.6	11.7
31	Yes	1.2	1	13.5	8.9	18	19.9
32	No	1.2	1.3	2.7	3.3	8.6	8
33	Yes	1.2	3.1	1.8	3.1	5	9.6
35	No	1.7	1.8	3	1.9	9.6	7.1
36	Yes	0.3	0.7	1	4	4	7.9

Study 3: RAIR parameters: Acute ON/OFF change:

Pt ID	Responder	Latency ON	Latency OFF	Recovery time ON	Recovery time OFF	Total duration ON	Total duration OFF
21	Yes	5.4	1.6	2.9	4.5	11.3	9
23	No	2.8	2.5	1.7	2.6	5.6	7.2
24	Yes	0.4	0.8	2.6	6	8.7	20.7
30	Yes	1.1	0.7	5.7	7	11.7	15.2
33	Yes	1.4	3.1	7.7	3.1	11.7	9.6
35	No	1.8	0.8	1.9	2.6	7.1	7.1
36	Yes	0.7	0.6	4	3.8	7.9	8.6

Appendix 4: Study 4 data (Chapter 10)

Study 4: Patients and clinical results:

Pt ID	Sex	Age	Aetiology	EAUS	Stim (days)	Responder	Baseline Wexner	FU Wexner
28	f	47	Obstetric	Intact	21	yes	13	4
29	m	77	Idiopathic	Atrophy	21	no	9	14
31	f	49	Obstetric	Defect	21	yes	13	3
32	f	25	Obstetric	Intact	11	no	20	20
33	f	60	Post-STARR	Intact	21	yes	14	6
34	f	66	Scleroderma	Atrophy	21	yes	16	13
35	f	54	Idiopathic	Intact	21	no	19	18
36	f	66	Obstetric	Defect	21	yes	18	12

Study 4: Anal manometry and rectal sensory thresholds:

Pt ID	Baseline resting	FU resting	Baseline Squeeze	FU Squeeze	Baseline FS Vol	FU FS Vol	Baseline U Vol	FU U Vol	Baseline MTV Vol	FU MTV Vol	Baseline electric threshold	FU electric threshold
28	62	74	47	54	27	69	88	228	98	252	23	29
29	68	56	101	185	372	304	>400	>400	>400	>400	35.5	23
31	81	46	33	60	73	20	110	60	175	140	21.5	23
32	56	70	38	22	20	30	30	50	40	60	9.5	21
33	100	69	38	84	52	50	76	110	95	160	40.5	28
34	72	38	134	90	63	30	125	60	213	120	24.5	-
35	68	81	40	39	30	50	100	90	150	110	33	-
36	62	60	29	8	20	60	40	90	105	120	30	32

Study 4: MR results:

a) Anorectal angle:

Pt ID	Interval between wire removal and FU scan (min.)	Baseline ARA rest	Baseline ARA strain	Baseline Δ ARA	FU ARA rest	FU ARA strain	FU Δ ARA
28	20	148	156	8	126	147	21
29	20	116	116	0	119	119	0
31	15	130	143	13	136	146	10
32	720	108	134	26	113	148	35
33	20	117	140	23	107	136	29
34	15	109	150	41	103	141	38
35	28	127	137	10	140	138	-2
36	11	143	150	7	137	132	-5

b) Pelvic floor descent:

Pt ID	Baseline bladder (rest)	Baseline bladder (strain)	Baseline vagina (rest)	Baseline vagina (strain)	Baseline anorectal (rest)	Baseline anorectal (strain)	FU bladder (rest)	FU bladder (strain)	FU vagina (rest)	FU vagina (strain)	FU anorectal (rest)	FU anorectal (strain)
28	1.9	-0.4	5.7	2.5	-2.9	-5.6	2.7	-0.9	4.9	1.5	-1.7	-6.4
29	5.8	5.7	male	male	-1.2	-1.7	5.6	6	male	male	-2.3	-1.2
31	1.2	-1.9	2.1	-0.9	-1.8	-5.9	2.2	-1.2	3.4	0	-4.7	-6.4
32	2.4	0	3.2	0.6	-1.6	-3.9	1.9	0.9	3.5	2.4	-1.5	-4.2
33	1.9	-2.3	3.6	-1.3	-2.9	-6.1	2.2	-1.6	4.7	1.1	-1.9	-5.1
34	2.1	0	4.5	1.1	-2.6	-2.9	2.1	0	4	0.6	-2.2	-3.6
35	0	-3.7	3.6	0	-4.1	-9.4	0	-3.4	2.8	0	-6.2	-8.8
36	1.6	-3.3	3	-2	-2.7	-7.7	1.1	-3.1	2.3	-1.9	-4.3	-6.7

c) Rectal evacuation parameters:

Baseline:

Pt ID	Baseline emptying grade	Baseline duration to maximal evacuation	baseline surface area of contrast† at beginning of evacuation (cm^2)	Baseline surface area of contrast† at 30 sec from commencing evacuation (cm^2)	Baseline proportion of evacuated contrast at 30 sec (%)
28	1	27	39.9	6.2	84.5
29	4	no evacuation	44.4	44.4	0
31	2	79	16.9	10.1	40.2
32	4	no evacuation	30.5	28.3	7.2
33	3	47 §	30.6	30.98	0
34	1	24	34.7	4.2	87.9
35	3	123	42.5	38.4	9.6
36	1	16	17.8	6.4	64

† below the first rectal fold
§ this case excluded from analysis (outlying FU value)

Follow Up (Post-SNS):

Pt ID	FU emptying grade	FU duration to maximal evacuation	FU surface area of contrast† at beginning of evacuation (cm^2)	FU surface area of contrast† at 30 sec from commencing evacuation (cm^2)	FU proportion of evacuated contrast at 30 sec (%)
28	1	8	37	0	100
29	4	no evacuation	28.2	28.2	0
31	1	16	34.8	7.2	79.3
32	4	no evacuation	22.3	21.3	4.5
33	3	198 §	33.4	26.8	19.8
34	1	15	31.6	0	100
35	2	69	26.9	19.3	28.3
36	1	16	28.2	8.5	69.9

† below the first rectal fold
§ this case excluded from analysis (outlier)

Appendix 5: Consent forms

University College London Hospitals NHS
NHS Foundation Trust

GI Physiology Unit
Podium Level 2
University College Hospital
235 Euston Road
London NW1 2BU

Unit Director: Dr Anton Emmanuel BSc, MD, FRCP
Tel: 0845 155 5000 ext 73209
Fax: 020 7380 9239

CONSENT FORM

Centre Number:
Patient Identification Number for this study:

UCLH Project ID number:
Form version: 1.1

Title of project: Examination of the anorectal physiological changes associated with Sacral Nerve Stimulation

Name of Principal investigator : Dr Anton Emmanuel

Please initial box

1. I confirm that I have read and understood the information sheet dated 15th Jun 2009 (version 1.1) for the above study and have had the opportunity to ask questions. ☐
2. I confirm that I have had sufficient time to consider whether or not want to be included in the study ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities or from the NHS trust where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
5. I agree for you to inform my GP of my participation. ☐
6. I agree to take part in the above study. ☐

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1 form for Patient;
1 to be kept as part of the study documentation;
1 to be kept with hospital notes

University College London Hospitals NHS
NHS Foundation Trust

GI Physiology Unit
Podium Level 2
University College Hospital
235 Euston Road
London NW1 2BU

Unit Director: **Dr Anton Emmanuel BSc, MD, FRCP**
Tel: **0845 155 5000 ext 73209**
Fax: **020 7380 9239**

Centre Number:
Patient Identification Number for this study:

UCLH Project ID number:
Form version: 1.1

CONSENT FORM

Title of project: Examination of the anorectal physiological changes associated with Sacral Nerve Stimulation

Name of Principal investigator : Dr Anton Emmanuel

Name of patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher (to be contacted if there are any problems)	Date	Signature

Comments or concerns during the study

If you have any comments or concerns you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, UCL hospitals. Please quote the UCLH project number at the top this consent form.

1 form for Patient;
1 to be kept as part of the study documentation,
1 to be kept with hospital notes

University College London Hospitals NHS
NHS Foundation Trust

GI Physiology Unit
Podium Level 2
University College Hospital
235 Euston Road
London NW1 2BU

Unit Director: Dr Anton Emmanuel BSc, MD, FRCP
Tel: 0845 155 5000 ext 73209
Fax: 020 7380 9239

CONSENT FORM

Centre Number:
Patient Identification Number for this study:

UCLH Project ID number:
Form version: 1.1

Title of project: Pilot study examining the possible functional Pelvic MRI changes associated with temporary SNS

Name of Principal investigator: Dr Anton Emmanuel

Please initial box

1. I confirm that I have read and understood the information sheet dated 15th June 2009 (version 1.2) for the above study and have had the opportunity to ask questions. ☐
2. I confirm that I have had sufficient time to consider whether or not want to be included in the study ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities or from the NHS trust where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
5. I agree for you to inform my GP of my participation in the study. ☐
6. I agree to take part in the above study. ☐

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1 form for Patient;
1 to be kept as part of the study documentation,
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NHS Foundation Trust

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London NW1 2BU

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Patient Identification Number for this study:

UCLH Project ID number:
Form version: 1.1

CONSENT FORM

Title of project: Pilot study examining the possible functional Pelvic MRI changes associated with temporary SNS

Name of Principal investigator: Dr Anton Emmanuel

Name of patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher (to be contacted if there are any problems)	Date	Signature

Comments or concerns during the study

If you have any comments or concerns you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, UCL hospitals. Please quote the UCLH project number at the top this consent form.

1 form for Patient;
1 to be kept as part of the study documentation,
1 to be kept with hospital notes

Appendix6: Published paper

ORIGINAL CONTRIBUTION

Temporary Sacral Nerve Stimulation Alters Rectal Sensory Function: A Physiological Study

Mostafa R. E. Abdel-Halim, M.Sc.[1] • James Crosbie, F.R.C.S.[2]
Alec Engledow, F.R.C.S.[2] • Alastair Windsor, F.R.C.S.[2]
Charles R. G. Cohen, F.R.C.S.[2] • Anton V. Emmanuel, M.D.[1]

1 Department of Pelvic Floor and GI Physiology at University College London Hospital, London, United Kingdom
2 Department of Colorectal Surgery at University College London Hospital, London, United Kingdom

BACKGROUND: The indications for sacral nerve stimulation are increasing, but the mechanism remains poorly understood.

OBJECTIVE: This study aimed to examine the effect of sacral nerve stimulation on rectal compliance and rectal sensory function.

DESIGN: This was a prospective study.

SETTINGS: This study took place at a university teaching hospital.

PATIENTS: Twenty-three consecutive consenting patients (22 female; median age, 49 y) undergoing temporary sacral nerve stimulation for fecal incontinence were prospectively studied. Clinical response was assessed by the use of bowel diaries and Wexner scores.

MAIN OUTCOME MEASURES: Anal manometry, rectal compliance, volume and pressure thresholds to rectal distension (barostat), and rectal Doppler mucosal blood flow were measured before and at the end of stimulation.

RESULTS: Sixteen patients (70%) had a favorable clinical response. Median anal squeeze pressures increased with stimulation from 40 (range, 6–156) cmH_2O to 64 (range, 16–243) cmH_2O. Median rectal compliance did not significantly change with stimulation (prestimulation: 11.5 (range, 7.9–21.8) mL/mmHg, poststimulation: 12.4 (range, 6.2–22) mL/mmHg, $P = .941$). Rectal wall pressures associated with urge (baseline: 15.4 (range, 11–26.7) mmHg, poststimulation: 19 (range, 11.1–42.7) mmHg, $P = .054$) and maximal tolerated thresholds (baseline: 21.6 (8.5–31.9) mmHg, poststimulation: 27.1 (14.3–43.3) mmHg, $P = .023$) significantly increased after stimulation. Rectal Doppler mucosal blood flow did not significantly change with stimulation (baseline: 125.8 (69.9–346.8), poststimulation: 112.4 (50.2–404.1), $P = .735$). Changes in anal resting pressure and rectal wall pressures with stimulation were evident only in responders; however, changes in anal squeeze pressures were evident in both responders and nonresponders.

LIMITATIONS: The study reports results following short-term stimulation in a small but homogenous group of patients. A larger long-term study will follow.

CONCLUSION: Temporary sacral nerve stimulation does not change rectal compliance, but is associated with significant changes to the pressure thresholds of rectal distension. This, together with the observation that outcome is not related to sphincter integrity, supports the hypothesis of an afferent-mediated mechanism of action.

KEY WORDS: Sacral nerve stimulation; Neuromodulation; Fecal incontinence; Afferent function; Mechanism of action; Barostat.

The first usage of electric spinal cord stimulation to treat pain reported by Shealy et al[1] and Wall and Sweet[2] in 1967 opened up the field of electrotherapy as a therapeutic modality. The idea of this treatment was based on the work on pain pathways some years earlier by Melzack and Wall that lead to the "Gate Control Theory of pain."[3]

Financial Disclosure: None reported.

Presented at the meeting of the British Society of Gastroenterology, Liverpool, United Kingdom, March 14 to 17, 2010. Poster presentation at the European Society of Coloproctology Meeting, Sorrento, Italy, September 22 to 25, 2010. Poster presentation at United European Gastroenterology Week Meeting, Barcelona, Spain, October 23 to 27, 2010.

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Dis Colon Rectum 2011; 54: 1134–1140
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Concepts of electrotherapy have developed significantly since then, with sacral nerve stimulation (SNS) emerging as a therapeutic modality in the field of bladder dysfunction.[4–6] The technique was first applied to treat fecal incontinence (FI) in 1995.[7] Since this report, numerous case series have demonstrated positive clinical results in FI with various underlying etiology[8–14] leading to the recognition of this modality in most treatment algorithms and guidelines.

Despite this wide acceptance and application, the exact mechanisms of action remain poorly understood. Sheldon et al[15] reported cerebral cortical changes with temporary stimulation, whereas Gooneratne et al[16] showed normalization of the mucosal levels of substance P in patients who respond to stimulation. Curiously, studies of anorectal physiology have mostly failed to show consistent changes with stimulation. Most studies have demonstrated no change in resting pressure with stimulation,[7,8,12,17–22] but some have shown an increase.[9,11,23,24] With regard to the squeeze function, most studies have demonstrated an increase with stimulation,[7–9,11,12,18,23–25] whereas some have shown no change[19–22] or an unsustained increase.[17] Studies have, however, included patients with mixed etiologies of incontinence, occasionally including patients with spinal injury. Moreover, different authors have occasionally used different techniques of measurement in their studies.

The results of examining rectal distension thresholds with SNS were also inconsistent. Two studies demonstrated the reduction of those thresholds with stimulation,[22,25] whereas other studies showed an increase[11] or no change.[12,26] Compliance measurement is a reflection of the rectal wall distensibility, which is an important function of the rectum as a reservoir and an essential component of the continence mechanism. Although the results of rectal compliance measurements in patients with FI are variable,[27–29] rectal compliance remains an important marker of anorectal function and its contribution to the pathophysiology in these patients.[28]

The majority of the few studies that have examined rectal compliance in the context of SNS have used the rectal balloon infusion technique,[8,17,20,30] an inaccurate way of assessing the biomechanical properties of the rectum.[31,32] The aim of this prospective study was to definitively examine the effects of SNS on rectal physiology, including rectal compliance. We hypothesized that improved continence would be correlated specifically with an increase in rectal compliance.

PATIENTS AND METHODS

Patients and Clinical Assessment

All patients undergoing temporary SNS were symptomatic for at least 1 year, and all conservative measures, including dietary, pharmacological, and biofeedback treatments, had failed. Routine preoperative assessment included full clinical evaluation, anorectal physiology studies, and endoanal ultrasound. Weekly bowel diaries detailing the frequency of bowel movement, the episodes of incontinence, and stool consistency (for a 3-week period) and the Wexner Incontinence Questionnaires were completed by the patient before and during the temporary stimulation phase. In agreement with most authors,[7–9] a positive clinical response to stimulation was considered if there was at least 50% improvement in symptoms; however, patients' subjective impression on the state of their symptoms was also taken in consideration.

The study was approved by the Local Research Ethics Committee (Joint UCL/UCLH Committees on the Ethics of Human Research Reference 09/H0715/29 Dated September 4, 2009) and all patients provided their consent to participate.

SNS Techniques

A temporary stimulation wire was inserted into S3 or S4 sacral foramen with the use of the Medtronic Insertion Kit 3065U (Medtronic, Minneapolis, MN) under fluoroscopy guidance in the operating theater. The procedure was performed under either general or local anesthesia according to patient preference. Consequently, the choice of the wire placement site depended on the best motor or sensory response to acute stimulation. The wire was secured in situ with dressings and was connected to an external stimulator (Medtronic 3650 Test Stimulator, Medtronic). Stimulation parameters were set with a pulse rate of 210 ms, pulse frequency of 14 Hz, and amplitude just at the sensory threshold. Stimulation was continuous for the longest possible duration between 2 and 3 weeks.

Anal Manometry

This was performed before and on the last day of the temporary stimulation phase. Station pull-through anal manometry was performed by the use of an 8-channel water-perfused manometry catheter (Ardomore Healthcare, Bucks, UK) controlled by software supplied by Medical Measurement Systems (MMS, Enschede, Netherlands). A standard water perfusion rate of 0.6 mL/min was used to perfuse the single-use 8-channel manometry catheter (Ardomore Healthcare, Bucks, UK). The maximal pressure increase was used as the parameter of the squeeze function. The normal reference range in our laboratory varies according to age and sex and has been previously published.[33]

Rectal Compliance Measurement

Rectal compliance measurement was performed before and on the last day of the temporary stimulation phase with the use of the electromechanical barostat device (Distender II, G&J Electronics, Ontario, Canada) and an oversized noncompliant polyethylene bag (CT-BP500R, Mui Scientific Inc,

Ontario, Canada) which was 20 cm long and with the maximum volume of 600 mL. The 2 ends of the bag were fixed to a specially designed dual-lumen silicone catheter (Mui Scientific Inc, Ontario, Canada) that was then inserted into the rectum while the patient was lying in the left lateral position following the completion of anal manometry.

Isobaric distension protocol was used. The minimal distension pressure was first identified, and then the basal operating pressure was determined by the addition of 2 mmHg. A short sequence of distension for conditioning then followed. The index distension sequence was in 4-mmHg increments continuing up to a maximum of basal operating pressure + 40 mmHg.

The average volume and pressure values for each phase of the index distension sequence were then calculated and plotted into Prism 4.0 software (GraphPad Software Inc, La Jolla, CA). A tangent was then drawn to the steepest part of the resultant curve and its gradient was calculated, which resulted in the measurement of rectal compliance in milliliters per mmHg. The methodology used and the reference for normality (11.9 ± 4.1 mL/mmHg) were similar to previously validated studies.[34]

Assessment of Rectal Sensory Function

Rectal sensory thresholds to distension were assessed during the isobaric barostat intrarectal bag distension. Patients were asked to report when they first perceived the following sensations during the index barostat-bag distension: first sensation, urgency to defecate, and maximal tolerated volume. The volume and pressure at each threshold point were recorded for each patient.

Mucosal sensory thresholds to electric stimulation were tested by the use of a bipolar electrode (Gaeltech, Skye, Scotland) connected to an electrical stimulator (MMS, Enchende, Netherlands). Electrical stimulation was applied at 10 Hz with a pulse width of 0.5 ms and increased (up to a maximum of 50 mA) until the patient reported the perceived sensation. Normal rectal electrosensitivity ranges in our laboratory were considered to be 21.3 (range, 2.9–39.7) mA for males, and 30.0 (range, 7.0–53.0) mA for females.[33]

Rectal Doppler Mucosal Blood Flow (RDMBF) Measurement

A DRT4 laser Doppler flowmeter (Moor Instruments, Devon, UK) was used. With the patient in the left lateral position, the probe was placed against the mucosa 10 cm above the lower limit of the anal margin. A recording was taken for 3 minutes after a stable reading was obtained. Normal reference range for the mean mucosal flux (155.4–210.2) was previously published.[35]

Statistical Analysis

StatsDirect statistical software package version 2.7.3 (StatsDirect, Cheshire, UK) was used for data analysis. Data were mainly presented as median and range. Baseline and post-stimulation results were compared using the Wilcoxon signed-rank test.

RESULTS

Twenty-three patients (22 females and 1 male) undergoing temporary SNS for intractable FI from April 2008 to February 2010 were studied.

Patients and Clinical Results

The median age of patients was 49 (range, 30–77). The etiology of FI included obstetric causes (12), idiopathic incontinence (5), postpelvic surgery (2), sphincter atrophy (1), scleroderma (1), subarachnoid hemorrhage (1), and long-standing rectal prolapse (1). All patients were experiencing at least weekly episodes of incontinence, and their symptoms were having a significant impact on their lifestyle; their mean Wexner scores were at 13.8 (± 2.8) (0 = perfect continence, 20 = worst possible incontinence).

All patients underwent endoanal ultrasound assessment at baseline. This showed intact sphincters in 13 patients (57%), atrophic sphincters in 4 (17%), and sphincter defects in 6 (26%). Sphincter repair had previously been performed in 9 patients (39%) of this cohort; 5 of them had residual defects. Only one patient with a sphincter defect diagnosed at the time of presentation did not undergo a repair procedure before SNS.

Sixteen patients (70%) had a significant clinical response to the stimulation; their weekly episodes of incontinence reduced from the mean of 5 (±2) to 1 (±2) ($P < .0001$). Their Wexner scores also significantly dropped from the mean of 14.1 (±3.1) to 6.3 (±4.4) ($P < .0001$). Nonresponders (7 patients, 30%) experienced some reduction in the number of weekly FI episodes (from 5 ± 2 to 3 ± 2, $P = .029$); however, the change in their Wexner incontinence scores (13.1 ± 2.1 to 12.7 ± 3.5; $P = .766$) was only marginal.

Clinical response was not influenced by the structural integrity of the sphincter as identified by endoanal ultrasound (χ^2 $P = .532$). The median duration of the temporary stimulation in the whole cohort was 21 days (range, 8–23); this did not differ between responders (21 days; range, 15–23) and nonresponders (21 days; range, 8–22) ($P = .899$, Mann Whitney) (Table 1).

Anal Manometry

Maximal squeeze pressure significantly increased with stimulation; from 40 (range, 6–156) cmH_2O to 65 (range, 16–243) cmH_2O ($P = .0003$). No significant increase in the resting pressure was demonstrated (Table 2). However, subgroup analysis revealed that resting pressures significantly improved in responders.

TABLE 1. Demographics and clinical data

	Responders n = 16	Nonresponders n = 7	P
Sex	16 female	6 female, 1 male	.664[a]
Age	48.5 (37–72)	50 (30–77)	.910[b]
Etiology of FI			
Obstetric	10	2	
Idiopathic	1	1	
Postpelvic surgery	2	0	
Sphincter atrophy	1	0	.078[a]
Scleroderma	1	0	
Subarachnoid hemorrhage	1	0	
Rectal prolapse	0	1	
Baseline Wexner scores	14.1 ± 3.1	13.1 ± 2.1	.483[c]
EAUS results			
Intact	9	1	
Atrophy	2	2	.532[a]
Defects	5	1	
Duration of stimulation	21 (15–23)	21 (8–22)	.899[b]
Follow up Wexner scores	6.3 ± 4.1	12.7 ± 3.5	**.0073**[c]

Bold indicates statistically significant *P* values.
FI = fecal incontinence; EAUS = endoanal ultrasound.
[a]χ^2 test.
[b]Mann-Whitney *U* test.
[c]Unpaired *t* test.

Rectal Compliance

Median baseline rectal compliance (11.5 (range, 7.9–21.8) ml/mmHg) did not significantly change after temporary SNS (12.4 (range, 6.2–22) mL/mmHg, $P = .941$). This was also the case when examining responders and nonresponders separately (Table 2).

Rectal Sensory Thresholds

Distension Thresholds. Maximal tolerated volumes were increased after stimulation. In addition, pressures associated with urgency and maximal tolerated distension were significantly increased. In the nonresponders (n = 6), this pattern of change in pressures was not seen (Table 3). There was no significant change in first sensation volumes or pressures or urgency volumes.

Electric Sensory Thresholds. Electric sensory thresholds did not change after SNS.

TABLE 2. Anal manometry and rectal compliance results

	Baseline[a]	Poststimulation[a]	P[b]
Resting pressure (cmH_2O)			
All (n = 23)	40 (16–113)	52 (16–119)	.098
Responders (n = 16)	39.5 (16–77)	50 (22–97)	**.051**
Nonresponders (n = 7)	58 (18–113)	52 (16–119)	0.813
Squeeze pressure (cmH_2O)			
All (n = 23)	40 (6–156)	65 (16–243)	**.0003**
Responders (n = 16)	50 (14–156)	75.5 (25–243)	**.010**
Nonresponders (n = 7)	31 (6–142)	46 (16–185)	**.016**
Rectal compliance (mL/mmHg)			
All (n = 23)	11.5 (7.9–21.8)	12.4 (6.2–22)	.941
Responders (n = 16)	11.7 (7.9–19.1)	12.4 (6.2–22)	.782
Nonresponders (n = 7)	13.7 (9.4–21.8)	12.8 (7.7–18.8)	.469

Bold indicates statistically significant *P* values.
[a]Data presented as median (range).
[b]Wilcoxon signed-rank test.

TABLE 3. Rectal sensory thresholds

	Baseline[a]	Poststimulation[a]	P[b]
FS vol (mL)[c]			
All (n = 22)	66.5 (25–160)	71 (23–160)	.949
Responders (n = 16)	83.5 (25–160)	82 (23–160)	.706
Nonresponders (n = 6)	60.5 (29–100)	53 (31–104)	.844
U vol (mL)[c]			
All (n = 22)	131 (50–236)	144 (30–299)	.558
Responders (n = 16)	141.5 (50–236)	150 (30–299)	.719
Nonresponders (n = 6)	114.5 (77–150)	117 (70–149)	.588
MTV (mL)[c]			
All (n = 22)	175 (70–271)	190.5 (60–307)	**.043**
Responders (n = 16)	185 (70–271)	210 (60–307)	.144
Nonresponders (n = 6)	150 (120–240)	176 (145–265)	.094
FS press (mmHg)[c]			
All (n = 22)	11 (7–23.1)	11.1 (6.4–22.9)	.832
Responders (n = 16)	10.9 (7–23.1)	11 (6.4–22.9)	>.999
Nonresponders (n = 6)	14.6 (7.2–20)	13 (7.1–20.1)	.525
U press (mmHg)[c]			
All (n = 22)	15.4 (11–26.7)	19 (11.1–42.7)	**.054**
Responders (n = 16)	15.3 (11–26.7)	19 (11.1–42.7)	.08
Nonresponders (n = 6)	19.1 (11.3–24.1)	19.2 (14.6–27)	.525
MT press (mmHg)[c]			
All (n = 22)	21.6 (8.5–31.9)	27.1 (14.3–43.3)	**.023**
Responders (n = 16)	20.6 (8.5–31.8)	27.1 (14.3–43.3)	**.058**
Nonresponders (n = 6)	23.4 (14.9–31.9)	25 (19–38.8)	.313
Electric thresholds (mA)			
All (n = 23)	20 (12–36.5)	23 (9.5–40)	.903
Responders (n = 16)	20.3 (12–28)	23 (9.5–34.5)	.831
Nonresponders (n = 7)	19.5 (16–36.5)	23 (19.5–40)	>.999

Bold indicates statistically significant *P* values.
FS vol = first sensation volume; U vol = urgency volume; MTV = maximal tolerated volume; FS press = first sensation pressure, U press = urgency pressure, MT press = maximal tolerated pressure.
[a]Data presented as median (range).
[b]Wilcoxon signed-rank test.
[c]Data of a nonresponder was excluded because of hindgut denervation.

RDMBF Results

There was a slight reduction in the Doppler mucosal blood flow readings following stimulation, but the magnitude of this reduction did not reach statistical significance (Table 4).

DISCUSSION

SNS has become widely accepted in the treatment of FI. However, an uncertainty remains as to its mechanisms of

TABLE 4. Doppler rectal mucosal blood flow

	Baseline[a]	Poststimulation[a]	P[b]
All patients (n = 23)	125.8 (60.9–346.8)	112.4 (50.2–404.1)	.735
Responders (n = 16)	125.4 (69.9–346.8)	113 (89.2–404.1)	>.999
Nonresponders (n = 7)	150.8 (85.5–205.6)	111.8 (50.2–156.9)	.75

[a]Data presented as median (range).
[b]Wilcoxon signec-ranktest.

action. Our study was undertaken to address the potential for sensory changes following SNS. In a landmark study of the latency of the sphincter response to acute stimulation of the sacral nerves, Fowler at al[36] demonstrated that it was much longer than would be expected if it was the result of direct stimulation of the efferent motor fibers, suggesting a complex multisynaptic pathway. The results of our study demonstrate changes to rectal sensory function. Such changes are thought to be transmitted via autonomic pathways. We have also shown an increase in the pressures associated with urgency and maximal tolerated distension, which might be indicative of changes in rectal wall tension and upregulation of mechanoreceptors in the pelvic floor.

Most previous studies have demonstrated an increase in the sphincter squeeze pressure with SNS,[7–9,11,17,18,23–25] although some have shown no change.[19–22] We have shown definite changes in voluntary squeeze pressure in all patients. As such, our study is in agreement with the majority of the physiological data, suggesting that there is a motor outcome following SNS. However, the elevation of pressures in both responders and nonresponders suggests that this mechanism may not be central to its therapeutic benefit. The effects on the resting sphincter pressure, which is mainly under tonic autonomic input, were less clear. Our study has suggested that, in responders only, there is an increase in resting sphincter pressure. The role of the autonomic nervous system is critical to resting internal anal sphincter tone, and it is possible that this autonomic input is moderated by SNS.

The maintenance of continence is a complex process that involves more than just an intact muscular sphincter. Normal rectal sensory function and rectal compliance are crucially important factors, and this study was designed to examine the potential changes to those physiological rectal properties as a result of SNS. Only few studies have examined rectal compliance with SNS, and only 3 have used the more accurate method of the electromechanical barostat device.[11,22,26] We used this technique, which has been shown to have good day-to-day and center-to-center reproducibility for measurement of rectal compliance.[34,37,38]

Baseline rectal compliance in this group of incontinent patients was within normal range. However, it was believed that a potential alteration of rectal compliance, albeit within the normal range, could still be a contributing underlying mechanism to symptom change in patients with FI. However, our study has shown that stimulation is not associated with a change in rectal compliance. This finding makes it difficult to understand the exact influence that SNS has on the autonomic function of the anorectum, because autonomic influence on the bowel does alter motility and tone, which are aspects closely linked to compliance. Moreover, in this study, RDMBF did not significantly change when measured after the period of temporary stimulation in contrast to what was shown by Kenefick et al.[39] However, that study was conducted on patients with indwelling permanent devices and examined the effect of acute change of the stimulation status or fluctuation of the stimulation levels rather than changes over a period of time.

Although the etiology of incontinence in the cohort of patients in this study is diverse, these patients represented a homogenous similar symptom profile, and reflected "real life" practice. It is possible that the different etiologies might influence baseline physiological parameters and, hence, the putative effects of SNS. For obvious reasons, the effects of SNS cannot be studied on healthy controls. However, Morren et al[40] examined the effects of an electric current generated over the sacrum by the use of a magnetic field in healthy controls, individuals with FI, and patients with spinal injury on anorectal physiology. They demonstrated an increase in anal pressures in all controls, but did not provoke such an increase in a quarter of the FI patients, raising the possibility that destruction of certain neuronal pathways in those patients made the stimulation unsuccessful.

Another limitation of our study is that the subject numbers are low. Inevitably, therefore, we cannot exclude the fact that some of the changes seen may reflect a type II statistical error. The fact that the majority of individuals respond to temporary stimulation means that comparison between such nonresponders and responders is even more problematic. We are using this current study to inform a larger long-term study that is under way at our institution. This will address both the persistence of SNS-induced changes with time, as well as the issue surrounding study group size. Such studies of chronic stimulation are much needed, especially because the reported discrepancy between the rates of clinical success with temporary and permanent SNS[12] might suggest that a difference exists in the underlying mechanisms involved during each stage. Nevertheless, this discrepancy might just be the result of an erroneous overselection of responders following the temporary phase.

The lack of a "biological" marker of response to temporary stimulation means that the assessment of response remains based merely on a change in symptoms, a process that, although widely used clinically, is potentially associated with error and subjectivity. This general inability to

identify a consistent physiological marker of a specific mechanism of action could raise the possibility of a mainly placebo effect associated with successful SNS. Alternatively, this may reflect an inadequacy of the tools available in studying anorectal physiological changes. The recent technological developments introducing high-resolution manometry techniques and detailed functional imaging might change this in the near future.

CONCLUSION

This study, and the review of the literature of studies that have attempted to understand the anorectal physiological changes associated with SNS, shows that the only consistent findings are the modest increase in the voluntary sphincter function and the suggestion of an alteration to the rectal sensory functions. Further work should attempt to examine the influence on the intrinsic nerve function. Because more techniques are now available to functionally examine the central nervous system, further efforts at assessing the influence at higher levels of the gut-brain axis should be made. This will hopefully lead to the isolation of a biological marker of positive clinical response and a clear understanding of the mechanisms of action involved, which will subsequently improve the process of prescription and patient selection for this costly treatment.

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